06-23-03 #9 DAC

AHP98970 N5

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WYETH

In re: U.S. Patent No. 5,563,146

Issued: October 8, 1996

Titled: METHOD OF TREATING HYPERPROLIFERATIVE VASCULAR DISEASE

Inventors: RANDALL E. MORRIS and CLARE R. GREGORY

Customer Number: 25291

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an application pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.710 *et seq.* to extend the term of Morris et al. U.S. Patent No. 5,563,146, which patent is owned by Wyeth. Assignment of the patent from the inventors to American Home Products Corporation is recorded at Reel 007077, Frame 0687. American Home Products Corporation changed its name to Wyeth, recordal of which is at Reel 012822, Frame 0248.

CERTIFICATE OF MAILING 37 CFR §1.10

I hereby certify that this paper and the documents referred to as enclosed therein are being deposited with the United States Postal Service on the date written below in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EV100601952US addressed to Mail Stop Patent Ext., Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

6-20-03
Date

Regina Benson
Regina Benson

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Pursuant to 37 C.F.R. §1.730(c), this application is being filed by Wyeth, the patent owner.

The requisite information pursuant to subparts (1) - (15) of 37 C.F.R. §1.740(a) is as follows:

(1) Identification of the Approved Product

The approved product is a medical device, the CYPHER™ sirolimus-eluting Coronary Stent, which is a combination product comprised of two regulated components: a device (stent system) and a drug product. The device component consists of a stent mounted onto a stent delivery system. The drug component is sirolimus (also known as rapamycin). A coating of the drug component and inactive ingredients is adhered to the surface of the stent.

(2) Identification of the Provision of Law under Which Regulatory Review Occurred

Regulatory review occurred under Section 515 and 520 (g) of the Federal Food, Drug and Cosmetics Act.

(3) The Date on Which the Product Received Permission for Commercial Marketing or Use under Section 515 of the Federal Food, Drug and Cosmetics Act.

Approval under Section 515 of the Federal Food, Drug and Cosmetics Act was received on April 24, 2003.

(4) Identification of Active Ingredient for Drug Products

Identification of an active ingredient is not believed to be required as the FDA

approved product is a medical device, and not a "drug product", within the meaning of 35 U.S.C. §156(f).

For the sake of clarity, the approved product is a combination product comprised of two regulated components: a device (stent system) and a drug component. The drug component includes the active ingredient sirolimus (also known as rapamycin). Sirolimus has been previously approved under Section 505 of the Federal Food, Drug and Cosmetics Act for commercial marketing or use for the prevention of organ rejection following renal transplantation.

(5) Statement of Timely Filing

This application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720 (f). The last day on which the application could be submitted is June 23, 2003.

(6) Identification of the Patent

The patent for which an extension is being sought is Morris et al. U.S. Patent No. 5,563,146, issued October 8, 1996. The inventors are Randall E. Morris and Clare R. Gregory. The date of expiration of the patent is April 28, 2012, based on a terminal disclaimer, under which the term of this patent will not extend beyond the expiration date of Pat. No. 5,188,711. US Patent 5,188, 711 expires 20 years from its April 28, 1992 filing date.

(7) Copy of Patent

A copy of Morris et al. U.S. Patent No. 5,536,146, including the entire specification, claims and drawings is submitted herewith as Exhibit A.

(8) Copy of Disclaimer, et al.

Copies of the applicable terminal disclaimer and receipt of maintenance fee payment are attached hereto as Exhibits B and C. No certificate of correction or reexamination certificate have been obtained.

(9) Statement Regarding Patent Claims

The patent claims a method of using the approved product.

The applicable claim is claim 1, which reads on the method of using the approved product as follows:

Claim 1 of U.S. Patent No. 5,543,146	Use of Approved Product
A method of preventing restenosis in a mammal	As reported in the Instructions for Use (IFU) and the Patient Information Guide for the CYPHER™ stent (a copy of which are attached hereto as exhibit D), in particular with respect to the results of the SIRIUS trial reported at Table 8-2 of the IFU, human patients receiving the approved product exhibited a significant reduction in the rate of binary restenosis and loss of mean lumen diameter.
resulting from said mammal undergoing a vascular catheterization, vascular scraping, vascular surgery, or laser treatment procedure	See IFU at Paragraph 12.5, step 2, where the operator is instructed to perform a vascular catheterization, predilating the vessel with a PTCA catheter.
which comprises administering an antirestenosis effective amount of rapamycin to said mammal orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via a vascular stent impregnated with rapamycin.	See IFU at p.3. The CYPHER™ stent is a vascular (coronary) stent having an effective amount of sirolimus (also known as rapamycin) adhered to the surface of the stent. In addition, the Sirolimus is administered intravascularly via a stent delivery catheter.

(10) Relevant Dates and Information Pursuant to 35 U.S.C. 156(g).

The relevant dates and information sufficient to enable the Secretary of Health and Human Services to determine the regulatory review period under 35 U.S.C. §156(g) for a medical device are as follows:

(A) The effective date of the investigational device exemption (IDE) was February 1, 2001 the date on which it received conditional approval. The IDE number was G000291/A1.

(B) The application for product approval was initially submitted on June 28, 2002 as Application No. P020026.

(C) The application was approved on April 24, 2003

(11) Brief Description of the Significant Activities Undertaken by the Marketing Applicant During the Regulatory Review Period with Respect to the Approved Product and the Significant Dates Applicable to Such Activities.

The Marketing Applicant during the regulatory review period was Cordis Corporation, a wholly owned subsidiary of Johnson & Johnson. Cordis Corporation is the licensee of Wyeth regarding U.S Patent 5,563,146.

The relevant significant communications of substance (all via letter unless otherwise noted) with the FDA and the dates related to such communications are identified below in tabular form:

DATE	TO	FROM	DESCRIPTION
November 3, 2000	FDA	Cordis	Submission of Investigative Device Exemption (IDE)
December 6, 2000	Cordis	FDA	Disapproval of IDE
December 29,2000	FDA	Cordis	IDE Amendment
January 19, 2001	FDA	Cordis	IDE Amendment
February 1, 2001	Cordis	FDA	Conditional approval of IDE
February 9, 2001	FDA	Cordis	Submission of IDE Supplement
February 20, 2001	FDA	Cordis	Submission of IDE Supplement
February 21, 2001	FDA	Cordis	Submission of IDE Supplement
March 22, 2001	FDA	Cordis	Submission of IDE Supplement
March 28, 2001	FDA	Cordis	Submission of IDE Supplement
April 19, 2001	Cordis	FDA	Conditional approval of IDE

DATE	TO	FROM	DESCRIPTION
May 2, 2001	FDA	Cordis	Submission of IDE Supplement
May 4, 2001	FDA	Cordis	Submission of IDE Supplement
May 11, 2001	Cordis	FDA	Conditional approval of IDE
May 18, 2001	FDA	Cordis	Submission of IDE Supplement
May 21, 2001	FDA	Cordis	Submission of IDE Supplement
May 25, 2001	FDA	Cordis	Submission of IDE Supplement
June 20, 2001	Cordis	FDA	Conditional approval of IDE
June 21, 2001	FDA	Cordis	Submission of IDE Supplement
June 25, 2001	FDA	Cordis	Submission of IDE Supplement
June 27, 2001	Cordis	FDA	Conditional approval of IDE
July 20, 2001	FDA	Cordis	Submission of IDE Supplement
August 16, 2001	Cordis	FDA	Approval of IDE
June 28, 2002	FDA	Cordis	Application for product approval (PMA)
July 9, 2002	FDA	Cordis	Submission of PMA Amendment
July 15, 2002	FDA	Cordis	Submission of PMA Amendment
July 24, 2002	FDA	Cordis	Submission of PMA Amendment
August 9, 2002	FDA	Cordis	Submission of PMA Amendment
August 14, 2002	FDA	Cordis	Submission of PMA Amendment
August 26, 2002	FDA	Cordis	Submission of PMA Amendment

DATE	TO	FROM	DESCRIPTION
September 3, 2002	FDA	Cordis	Submission of PMA Amendment
September 9, 2002	FDA	Cordis	Submission of PMA Amendment
September 26, 2002	FDA	Cordis	Submission of PMA Amendment
October 3, 2002	FDA	Cordis	Submission of PMA Amendment
October 21, 2002	FDA	Cordis	Submission of PMA Amendment
October 22, 2002	Meeting		Circulatory System Device Panel Meeting
December 13, 2002	FDA	Cordis	Submission of PMA Amendment
December 31, 2002	FDA	Cordis	Submission of PMA Amendment
February 4, 2003	FDA	Cordis	Submission of PMA Amendment
February 13, 2003	FDA	Cordis	Submission of PMA Amendment
February 21, 2003	FDA	Cordis	Submission of PMA Amendment
February 25, 2003	FDA	Cordis	Submission of PMA Amendment
March 3, 2003	FDA	Cordis	Submission of PMA Amendment
March 20, 2003	FDA	Cordis	Submission of PMA Amendment
March 24, 2003	FDA	Cordis	Submission of PMA Amendment
April 4, 2003	FDA	Cordis	Submission of PMA Amendment
April 14, 2003	FDA	Cordis	Submission of PMA Amendment
April 21, 2003	FDA	Cordis	Submission of PMA Amendment
April 24, 2003	Cordis	FDA	Device Approval Letter

(12) Statement That the Patent Is Eligible for an Extension of 557 Days

In the opinion of the Applicant, U.S. Patent No. 5,563,146 is eligible for an extension of 557 days:

1. The term of U.S. Patent No. 5,563,146 has never been extended.
2. The application for extension of patent term is submitted by Wyeth, the owner of the patent.
3. The medical device has been subject to regulatory review prior to commercial marketing or use.
4. The device received permission for commercial marketing on April 24, 2003 which is less than 60 days prior to the filing of this application.
5. No other patent term has been extended for the same regulatory review period for this device.

The claimed extension of 557 days was determined as being the sum of the testing and approval periods, less one-half of the days in the testing period. In the present case, the pertinent dates are:

Patent issued:	October 8, 1996
Testing period began:	February 1, 2001
Application submitted:	June 28, 2002
FDA approval:	April 24, 2003

Calculation of the total extension of time pursuant to 37 C.F.R. §1.777 is according to the formula:

$$\text{Period of Term Extension (PTE)} = 1/2\ (X - D_1) + (Y - D_2)$$

where:

X = days of testing phase,

D_1 = days where applicant did not act with diligence in testing phase,

Y = days of approval phase, and

D_2 = days where applicant did not act with diligence in approval phase.

Thus, where X is 514 days (from February 1, 2001 to the June 28, 2002 application), Y is 300 days (from June 28, 2002 to April 24, 2003) and D_1 and D_2 are 0:

PTE = 1/2 (514 - 0) + (300 - 0);

PTE = 557 days

This term extension should run from the effective April 28, 2012 expiration date set by the terminal disclaimer. 37 C.F.R. §1.777(a).

The 14-year limit of 35 U.S.C. §156(c)(3) and 37 C.F.R. §1.777(d)(3) does not affect the patent term extension. The extended period added to the April 28, 2012 original patent expiration ends November 6, 2013, which is before April 24, 2017 (14 years from the April 24, 2003 FDA approval).

Inasmuch as the patent term extension is less than five years, the five year limit of 35 U.S.C. §156(g)(6)(A) and 37 C.F.R. §1.777(5) also does not affect the patent term extension.

The 2-year limit of 35 U.S.C. §156(g)(6)(C) does not apply. U.S. Patent No. 5,563,146 issued October 8, 1996, which is after the date of enactment of 35 U.S.C. §156.

(13) Acknowledgment of the Duty of Disclosure

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the

Secretary of Agriculture any information material to the determination of entitlement to the extension sought.

(14) Fee

The prescribed $1,120.00 fee for receiving and acting upon the application for extension is submitted herewith. If the fee is determined to be higher or lower than that submitted herewith, the PTO is hereby authorized to charge or credit Deposit Account No. 01-1425 for any such amount.

(15) Contact for Inquiries and Correspondence

Inquiries and correspondence relating to the application for patent term extension are to be directed to:

Thomas S. Szatkowski
Wyeth
Five Giralda Farms
Madison, NJ 07940
973-660-7649

A Power of Attorney from Wyeth is attached as Exhibit E.

(16) Duplicate Copies

This application is being submitted herewith with two additional copies (for a total of three copies) pursuant to the requirements of 37 C.F.R. §1.740(b).

Thomas S. Szatkowski
Registration No. 28,049
Attorney for Applicant, Wyeth

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Exhibit A

US005563146A

United States Patent [19]

Morris et al.

[11] Patent Number: 5,563,146

[45] Date of Patent: *Oct. 8, 1996

[54] METHOD OF TREATING HYPERPROLIFERATIVE VASCULAR DISEASE

[75] Inventors: Randall E. Morris, Los Altos; Clare R. Gregory, Menlo Park, both of Calif.

[73] Assignee: American Home Products Corporation, Madison, N.J.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,288,711.

[21] Appl. No.: 452,051

[22] Filed: May 26, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 238,305, May 12, 1994, Pat. No. 5,516,781, which is a continuation-in-part of Ser. No. 980,000, Nov. 23, 1992, abandoned, which is a continuation of Ser. No. 819,314, Jan. 9, 1992, abandoned.

[51] Int. Cl.[6] A61K 31/71

[52] U.S. Cl. 514/291; 424/122

[58] Field of Search 514/291; 424/122

[56] References Cited

U.S. PATENT DOCUMENTS

3,929,992	12/1975	Sehgal et al.	424/122
4,885,171	12/1989	Surendra et al.	424/122
5,078,999	1/1992	Warner et al.	424/122
5,080,899	1/1992	Sturm et al.	424/122
5,100,899	3/1992	Calne	514/291
5,252,579	10/1993	Skotnicki	514/291
5,256,790	10/1993	Nelson	514/291
5,288,711	2/1994	Mitchell	514/56

FOREIGN PATENT DOCUMENTS

A20401747	6/1990	European Pat. Off. .

OTHER PUBLICATIONS

Gregory C. R., et al., American Society of Transplant Physicians, 13th Annual Meeting, May 16–18, 1994; Abstract (38) 9, mailed to attendees Apr. 27, 1994.

Gregory C. R., et al., American Society of Transplant Physicians, 13th Annual Meeting, May 16–18, 1994; Abstract (38) 10, mailed to attendees Apr. 27, 1994.

Gregory C. R., et al., Transplantation Proceedings, 25:1, 120–121 (Feb. 1993).

Gregory C. R., et al., Transplantation Proceedings, 25:1, 770–771 (Feb. 1993).

Gregory C. R., et al., Transplantation, 55:1409–1418 (Jun. 1993).

Gregory C. R., et al., Veterinary Surgery, Abstract 11:40 (Jan. 1993).

Gregory C. R. et al., J. Heart and Lung Transplantation, Abstract 27, 11:197 (1992).

Gregory C. R. et al., FASEB, Abstract 21, 6:A940 (1992).

Meiser, B. M. et al., J. Heart and Lung Transplantation, Abstract 3, 9:55 (1990).

Meiser, B. M. et al., Lancet 338:1297–1298 (1991).

Ferns, G. A. et al., Circulation, Abstract 0727, 80 (Supp. II) 183 (1989).

Jonasson, L. et al., Proc. Natl. Acad. Sci., 85:2303–2306 (Apr. 1988).

Morris, P. J. et al., Transplantation Reviews, 6:39 (1992).

Staruch, M. J., FASEB 3:3411 (1989).

Martel, R. R., Canadian Journal of Physiol. Pharmacology, 55:48 (1977).

Morris, R. E., Med. Sci. Res. 17:877 (1989).

Baeder, W. L., Fifth Int. Conf. Inflamm. Res. Assoc. 121 (Abstract) (1990).

Eng, C. P. et al., The Journal of Antiboitics, 37:1231 (1984).

The Merck Index, 9th ed., 6152:829–821 (1976).

Weaver, J. L., J. Cell Biology, Abstract 1308, 111:(5 Part 2)234a.

Transplantation Proc. 23:2833 (1991).

Cytokine 3:472 (1991).

Transplantation Proc. 23:507 (1991).

Transplantation 50:554 (1990).

Immunology 72:544 (1991).

Ferns, G., Am. J. Path. 137:403 (1990).

Transplantation Proc. 23:2833 (1991).

Primary Examiner—Michael G. Wityshyn
Assistant Examiner—Jean C. Witz
Attorney, Agent, or Firm—Arnold S. Milowsky

[57] ABSTRACT

This invention provides a method of preventing or treating hyperproliferative vascular disease in a mammal by administering an antiproliferative effective amount of rapamycin alone or in combination with mycophenolic acid.

4 Claims, No Drawings

METHOD OF TREATING HYPERPROLIFERATIVE VASCULAR DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation of application Ser. No. 08/238,305 filed May 12, 1994, now U.S. Pat. 5,516,781 which is a continuation-in-part of U.S. Ser. No. 07/980,000 filed Nov. 23, 1992, abandoned, which is a continuation of U.S. Ser. No. 07/819,314 filed Jan. 9, 1992, abandoned.

BACKGROUND OF THE INVENTION

Many individuals suffer from heart disease caused by a partial blockage of the blood vessels that supply the heart with nutrients. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Typically vascular occlusion is preceded by vascular stenosis resulting from intimal smooth muscle cell hyperplasia. The underlying cause of the intimal smooth muscle cell hyperplasia is vascular smooth muscle injury and disruption of the integrity of the endothelial lining. The overall disease process can be termed a hyperproliferative vascular disease because of the etiology of the disease process. Intimal thickening following arterial injury can be divided into three sequential steps: 1) initiation of smooth muscle cell proliferation following vascular injury, 2) smooth muscle cell migration to the intima, and 3) further proliferation of smooth muscle cells in the intima with deposition of matrix. Investigations of the pathogenesis of intimal thickening have shown that, following arterial injury, platelets, endothelial cells, macrophages and smooth muscle cells release paracrine and autocrine growth factors (such as platelet derived growth factor, epidermal growth factor, insulin-like growth factor, and transforming growth factor) and cytokines that result in the smooth muscle cell proliferation and migration. T-cells and macrophages also migrate into the neointima. [Haudenschild, C., *Lab. Invest.* 41:407 (1979); Clowes, A., *Circ. Res.* 56:139 (1985); Clowes, A., J, *Cardiovas. Pharm.* 14 (Suppl. 6): S12 (1989); Manderson, J., Arterio. 9:289 (1989); Forrester, J., *J. Am. Coll. Cardiol.* 17:758 (1991)]. This cascade of events is not limited to arterial injury, but also occurs following injury to veins and arterioles.

Vascular injury causing intimal thickening can be broadly categorized as being either biologically or mechanically induced. Artherosclerosis is one of the most commonly occurring forms of biologically mediated vascular injury leading to stenosis. The migration and proliferation of vascular smooth muscle plays a crucial role in the pathogenisis of artherosclerosis. Artherosclerotic lesions include massive accumulation of lipid laden "foam cells" derived from monocyte/macrophage and smooth muscle cells. Formation of "foam cell" regions is associated with a breech of endothelial integrity and basal lamina destruction. Triggered by these events, restenosis is produced by a rapid and selective proliferation of vascular smooth muscle cells with increased new basal lamina (extracellular matrix) formation and results in eventual blocking of arterial pathways. [Davies, P. F.; *Artherosclerosis Lab. Invest.* 55:5 (1986)].

Mechanical injuries leading to intimal thickening result following balloon angioplasty, vascular surgery, transplantation surgery, and other similar invasive processes that disrupt vascular integrity. Intimal thickening following balloon catheter injury has been studied in animals as a model

for arterial restenosis that occurs in human patients following balloon angioplasty. Clowes, Ferns, Reidy and others have shown that deendothelilization with an intraarterial catheter that dilates an artery injures the innermost layers of medial smooth muscle and may even kill some of the innermost cells. [Schwartz, S. M., *Human Pathology* 18:240 (1987); Fingerle, J., *Ateriosclerosis* 10:1082 (1990)] Injury is followed by a proliferation of the medial smooth muscle cells, after which many of them migrate into the intima through fenestrae in the internal elastic lamina and proliferate to form a neointimal lesion.

Vascular stenosis can be detected and evaluated using angiographic or sonographic imaging techniques [Evans, R. G., *JAMA* 265:2382 (1991)] and is often treated by percutaneous transluminal coronary angioplasty (balloon catheterization). Within a few months following angioplasty, however, the blood flow is reduced in approximately 30–40 percent of these patients as a result of restenosis caused by a response to mechanical vascular injury suffered during the angioplasty procedure, as described above. [Pepine, C., *Circulation* 81:1753 (1990); Hardoff, R., *J. Am. Coll. Cardiol.* 15 1486 (1990)].

In an attempt to prevent restenosis or reduce intimal smooth muscle cell proliferation following angioplasty, numerous pharmaceutical agents have been employed clinically, concurrent with or following angioplasty. Most pharmaceutical agents employed in an attempt to prevent or reduce the extent of restenosis have been unsuccessful. The following list identifies several of the agents for which favorable clinical results have been reported: lovastatin [Sahni, R., *Circulation* 80 (Suppl.) 65 (1989); Gellman, J., *J. Am. Coll. Cardiol.* 17:251 (1991)]; thromboxane A_2 synthetase inhibitors such as DP-1904 [Yabe, Y., *Circulation* 80 (Suppl.) 260 (1989)]; eicosapentanoic acid [Nye, E., *Aust. N.Z. J. Med.* 20:549 (1990)]; ciprostene (a prostacyclin analog) [Demke, D., *Brit. J. Haematol* 76 (Suppl.): 20 (1990); Darius, H., *Eur. Heart J.* 12 (Suppl.): 26 (1991)]; trapidil (a platelet derived growth factor) [Okamoto, S., *Circulation* 82 (Suppl.): 428 (1990)]; angiotensin converting enzyme inhibitors [Gottlieb, N., *J. Am. Coll. Cardiol.* 17 (Suppl. A): 181A (1991)]; and low molecular weight heparin [de Vries, C., *Eur. Heart J.* 12 (Suppl.): 386 (1991)].

In an attempt to develop better agents for preventing or reducing smooth muscle proliferation and intimal thickening, the use of balloon catheter induced arterial injury in a variety of mammals has been developed as a standard model of vascular injury that will lead to intimal thickening and eventual vascular narrowing. [Chevru, A., *Surg. Gynecol. Obstet.* 171:443 (1990); Fishman, J., *Lab. Invest.* 32:339 (1975); Haudenschild, C., *Lab. Invest.* 41:407 (1979); Clowes, A. W., *Lab. Invest.* 49:208 (1983); Clowes, A. W., *J. Cardiovas. Pharm.* 14:S12 (1989); and Ferns, G. A., *Science* 253:1129 (1991)]. Many compounds have been evaluated in this standard animal model. The immunosuppressive agent cyclosporin A has been evaluated and has produced conflicting results. Jonasson reported that cyclosporin A caused an inhibition of the intimal proliferative lesion following arterial balloon catheterization in vivo, but did not inhibit smooth muscle cell proliferation in vitro. [Jonasson, L., *Proc. Natl. Acad. Sci.* 85:2303 (1988)]. Ferns, however reported that when de-endothelilized rabbits were treated with cyclosporin A, no significant reduction of intimal proliferation was observed in vivo. Additionally, intimal accumulations of foamy macrophages, together with a number of vacuolated smooth muscle cells in the region adjacent to the internal elastic lamina were observed, indicating that cyclosporin A may modify and enhance lesions

that form at the sites of arterial injury. [Ferns, G. A., *Circulation* 80 (Supp): 184 (1989); Ferns, G., *Am. J. Path.* 137:403 (1990)].

Rapamycin, a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus* [U.S. Pat. No. 3,929,992] has been shown to prevent the formation of humoral (IgE-like) antibodies in response to an albumin allergic challenge [Martel, R., *Can. J. Physiol. Pharm.* 55:48 (1977)], inhibit murine T-cell activation [Staruch, M., *FASEB* 3:3411 (1989)], prolong survival time of organ grafts in histoincompatible rodents [Morris, R., *Med. Sci. Res.* 17:877 (1989)], and inhibit transplantation rejection in mammals [Calne, R., European Patent Application 401,747]. Rapamycin blocks calcium-dependent, calcium-independent, cytokine-independent and constitutive T and B cell division at the G1-S interface. Rapamycin inhibits gamma-interferon production induced by Il-1 and also inhibits the gamma-interferon induced expression of membrane antigen. [Morris, R. E., *Transplantation Rev.* 6:39 (1992)]. The use of rapamycin in preventing coronary graft atherosclerosis (CGA) in rats has been disclosed by Meiser [*J. Heart Lung Transplant* 9:55 (1990)]. Arterial thickening following transplantation, known as CGA, is a limiting factor in graft survival that is caused by a chronic immunological response to the transplanted blood vessels by the transplant recipient's immune system. [Dec. G, *Transplantation Proc.* 23:2095 (1991) and Dunn, M. *Lancet* 339:1566 (1992)]. The disclosed invention is distinct from the use of rapamycin for preventing CGA, in that CGA does not involve injury to the recipients own blood vessels; it is a rejection type response. The disclosed invention is related to vascular injury to native blood vessels. The resulting intimal smooth muscle cell proliferation dose not involve the immune system, but is growth factor mediated. For example, arterial intimal thickening after balloon catheter injury is believed to be caused by growth factor (PGDF, bFGF, TGFb, IL-1 and others)-induced smooth muscle cell proliferation and migration. [Ip, J. H., *J. Am. Coll. Cardiol* 15:1667 (1990)]. Ferns has also shown that the immune response is not involved in arterial intimal thickening following balloon catheterization, as he found that there was no difference in intimal thickening between arteries from athymic nude rats (rats lacking T-cells) and normal rats after balloon catheterization [*Am. J. Pathol.* 138:1045 (1991)].

DESCRIPTION OF THE INVENTION

This invention provides a method of preventing or treating hyperproliferative vascular disease in a mammal in need thereof by administering an antiproliferative effective amount of rapamycin to said mammal orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via a vascular stent impregnated with rapamycin.

As such, rapamycin is useful in treating intimal smooth muscle cell hyperplasia, restenosis, and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Biologically mediated vascular injury includes, but is not limited to injury attributed to infectious disorders including endotoxins and herpes viruses such as cytomegalovirus; metabolic disorders such as atherosclerosis; and vascular injury resulting from hypothermia, and irradiation. Mechanically mediated vascular injury includes, but is not limited to vascular injury caused by catheterization procedures or vascular scraping procedures such as percutaneous transluminal coronary angioplasty; vascular surgery; transplantation surgery; laser treatment; and other invasive procedures which disrupt the integrity of the vascular intima or endothelium. Rapamycin is also useful in preventing intimal smooth muscle cell hyperplasia, restenosis, and vascular occlusion resulting from mechanically mediated injury. In particular, for the prevention of restenosis following a percutaneous transluminal coronary angioplasty procedure.

Treating includes retarding the progression, arresting the development, as well as palliation. Preventing includes inhibiting the development of and prophylacticly preventing of hyperproliferative vascular disease in a susceptible mammal.

This invention also provides a method of using a combination of rapamycin and mycophenolic acid for the same utilities described above. Mycophenolic acid, an antiproliferative antimetabolite, inhibits inosine monophosphate dehydrogenase and guanosine monophosphate synthetase, enzymes in the de novo purine biosynthetic pathway. This results in an inhibition of DNA synthesis which causes an accumulation of cells at the G1-S interface. Other combinations containing rapamycin that are useful for preventing or treating hyperproliferative vascular disease will be apparent to one skilled in the art. These include, but are not limited to, using rapamycin in combination with other antiproliferative antimetabolites.

The effect of rapamycin on hyperproliferative vascular disease was established in an in vitro and an in vivo standard pharmacological test procedure that emulates the hyperproliferative effects observed in mammals that are undergoing intimal smooth muscle proliferation and are therefore developing restenosis. Cycloporin A was also evaluated in these test procedures for the purpose of comparison. The combination of rapamycin and mycophenolic acid was evaluated in the in vivo test procedure. The procedures and the results obtained are described below.

Rapamycin and cyclosporin A were evaluated in an in vitro standard pharmacological test procedure which emulates the intimal smooth muscle cell proliferation observed following vascular injury. Results were obtained by measuring DNA and protein synthesis in rat smooth muscle cells that have been stimulated with a growth factor such as fetal calf serum or a hypertrophic mitogen, such as angiotensin II. The following briefly describes the procedure that was used. Rat smooth muscle cells were maintained in a 1:1 mixture of defined Eagle's medium (DEM) and Ham's F12 medium with 10% fetal calf serum, penicillin (100 U/mL), streptomycin (100 mg/mL) and 25 mL Hepes at pH 7.4. Cells were incubated at 37° C. in a humidified atmosphere of 5% CO_2 with media changes every 2–3 days. Each compound tested was diluted with an appropriate vehicle to obtain a 1 mM stock solution. Ethanol was used as the vehicle for rapamycin and 20% tween 80 in ethanol was the vehicle for cyclosporin A. Test concentrations of drug were obtained by diluting appropriate concentrations of stock solution with serum free media. The smooth muscle cell culture was maintained in a defined serum free media containing 1:1 DEM and Ham's F12 medium, insulin (5×10^{-7}M), transferrin (5 μg/mL), and ascorbate (0.2 mM) for 72 hours before testing in a multi-well plate. After the 72 hour period, an appropriate quantity of stock solution containing either rapamycin or cyclosporin A was added to the smooth muscle cell culture and media mixture. After a 24 hours the appropriate growth factor was added. For the measurement of DNA synthesis, ^{3}H-thymidine was added at 12 hours after the growth factor was added, and the cells were harvested at 36 hours. For the measurement of protein synthesis, ^{3}H-leucine was added at 14 hours after the growth factor was added, and the cells were harvested at 18 hours. The amount

of incorporated radioactive label was measured on a scintillation counter.

The following table shows the results obtained for rapamycin on DNA and protein synthesis in smooth muscle cells that were stimulated with 10% fetal calf serum, as measured by incorporation of tritiated thymidine or leucine into smooth muscle cells. The amount of tritiated label incorporated by the smooth muscle cells that were treated with media only was normalized to 100%, and the results for cells treated with fetal calf serum or fetal calf serum plus the test compound are expressed as a percent comparison with the cells treated with media only.

EFFECT OF RAPAMYCIN ON DNA AND PROTEIN SYNTHESIS IN SMOOTH CELLS STIMULATED WITH FETAL CALF SERUM*

	^{3}H-Thymidine Incorporation (% of Media)	^{3}H-Leucine Incorporation (% of Media)
Media	100%	100%
FCS	495%	174%
1000 nM RAP + FCS	136%	95%
100 nM RAP + FCS	172%	91%
10 nM RAP + FCS	204%	74%
1 nM RAP + FCS	403%	106%

*Abbreviations: RAP = rapamycin; Media = defined serum free media; and FCS = 10% fetal calf serum.

The following table shows the results obtained for rapamycin on protein synthesis in smooth muscle cells that were stimulated with 10^{-6} nM angiotensin II, as measured by incorporation of tritiated leucine into smooth muscle cells. The amount of tritiated label incorporated by the smooth muscle cells that were treated with media only were normalized to 100%, and the results for cells treated with angiotensin or angiotensin plus the test compound are expressed as a percent comparison with the cells treated with media only.

EFFECT OF RAPAMYCIN ON PROTEIN SYNTHESIS IN SMOOTH CELLS STIMULATED WITH ANGIOTENSIN II*

	^{3}H-Leucine Incorporation (% of Media)
Media	100%
ANG	159%
1000 nM RAP + ANG	53%
100 nM RAP + ANG	57%
10 nM RAP + ANG	61%
1 nM RAP + ANG	60%

*Abbreviations: RAP = rapamycin; Media = defined serum free media; and ANG = 10^{-6} nM angiotensin II.

The results of the standard in vitro test procedure showed that rapamycin had a pronounced antiproliferative effect in the presence of FCS and an anti-hypertrophic effect in the presence of angiotensin II. Following vascular injury, DNA and protein synthesis of smooth muscle cells are necessary for the development of restenosis to occur. These results showed that rapamycin inhibited both DNA and protein synthesis in stimulated smooth muscle cells. An antiproliferative effect was also observed with cyclosporin A; however, at 1000 nM, cyclosporin A was cytotoxic and not merely cytostatic. At 1000 nM, cyclosporin A caused lysis of the smooth muscle cells as evidenced by the presence of lactic acid dehydrogenase in the supernatant of the cell culture. Similar toxicity to smooth muscle cells was not observed for rapamycin.

Rapamycin, rapamycin plus mycophenolic acid, and cyclosporin A were evaluated in an in vivo standard pharmacological test procedure that emulates the vascular injury suffered and restenosis that develops following percutaneous transluminal coronary angioplasty in humans. The ability of a test compound to inhibit restenosis was determined by comparing intimal thickening in mammals treated with test compound following balloon catheterization versus intimal thickening in untreated control mammals after the same test procedure. [Chevru, A., *Surg. Gynecol. Obstet.* 171:443 (1990); Fishman, J., *Lab. Invest.* 32:339 (1975); Haudenschild, C., *Lab. Invest.* 41:407 (1979); Clowes, A. W., *Lab. Invest.* 49:208 (1983); Clowes, A. W., *J. Cardiovas. Pharm.* 14:S12 (1989); and Ferns, G. A., *Science* 253:1129 (1991)]. The following briefly describes the procedure that was used. The left carotid arteries of male Sprague-Dawley rats were injured with an inflated 2 Fr balloon catheter. During a 14 day postoperative period, these rats were divided into groups and treated daily with rapamycin (1.5 mg/kg; i.p.), rapamycin plus mycophenolic acid (1.5 mg/kg; i.p.+40 mg/kg; p.o.), or cyclosporin A (3 mg/kg; i.p.). Treatment was administered on days 0 to 13 postoperatively. Additionally, one group each also received rapamycin (6 mg/kg/day; i.p.) or cyclosporin A (40 mg/kg/day; i.p.) for two days postoperatively, and then received no treatment for the next 12 days. An untreated group was used an injured control to establish the amount of intimal growth in the absence of treatment. The right carotid was used as an uninjured control in all groups. After the 14-day period, the rats were sacrificed, the carotids removed. The mean areas of the intima and blood vessel wall were measured by morphometry. Results are expressed as an intima percent which can be expressed according to the following formula:

$$\frac{\text{area of intima}}{\text{area of vessel}} \times 100$$

The following table shows the results that were obtained.

EFFECT OF RAPAMYCIN ON INTIMAL THICKENING IN INJURED CAROTID ARTERIES (DAY 14)*

Test Group	Intima Percent ± S.E.
Uninjured Control	0.00 ± 0.00
Untreated Injured Control	33.3 ± 19.66
RAP (1.5 mg/kg - 14 days)	6.78 ± 4.69
RAP (6 mg/kg - 2 days)	16.56 ± 6.22
RAP + MPA (14 days)	1.6 ± 3.5
CsA (3 mg/kg - 14 days)	26.46 ± 27.42
CsA (40 mg/kg - 2 days)	31.14 ± 20.66

*Abbreviations RAP = rapamycin; MPA = mycophenolic acid; and CsA = cyclosporin A.

These results show that treatment with rapamycin (1.5 mg/kg for 14 days) resulted in an 80% decrease in the mean percentage intimal thickening compared with the untreated injured control group. Similarly, treatment with the combination of rapamycin and mycophenolic acid produced almost a complete inhibition of intimal thickening (95% reduction in intimal thickening compared with untreated injured control). Cyclosporin A failed to produce any meaningful reduction in intimal thickening.

Similar results were obtained when rapamycin was evaluated at different doses in the above in vivo standard pharmacological test procedure that emulates the vascular injury that occurs following a percutaneous transluminal coronary angioplasty procedure in humans. Rapamycin was administered on postoperative days 0–13, and examination by

morphometry was performed on day 14. Rapamycin, at a dose of 1.5 and 3 mg/kg significantly arrested the development of restenosis as measured by the intima percent 14 days after balloon catheterization, whereas restenosis was clearly observed in the untreated injured control group. These results are summarized in the table below.

EFFECT OF RAPAMYCIN ON INTIMAL THICKENING IN INJURED CAROTID ARTERIES (DAY 14)

Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control			0.00 ± 0.00
Untreated Injured Control			44.51 ± 5.03
Rapamycin	6 mg/kg	0–13	30.92 ± 4.06
Rapamycin	3 mg/kg	0–13	22.68 ± 6.28
Rapamycin	1.5 mg/kg	0–13	21.89 ± 4.2

The results of the in vitro and in vivo standard test procedures demonstrate that rapamycin and rapamycin in combination with mycophenolic acid are useful in treating hyperproliferative vascular disease.

As such, rapamycin is useful in treating intimal smooth muscle cell hyperplasia, restenosis, and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Biologically mediated vascular injury includes, but is not limited to injury attributed to infectious disorders including endotoxins and herpes viruses such as cytomegalovirus; metabolic disorders such as atherosclerosis; and vascular injury resulting from hypothermia, and irradiation. Mechanically mediated vascular injury includes, but is not limited to vascular injury caused by catheterization procedures or vascular scraping procedures such as percutaneous transluminal coronary angioplasty; vascular surgery; transplantation surgery; laser treatment; and other invasive procedures which disrupt the integrity of the vascular intima or endothelium.

Rapamycin and rapamycin plus mycophenolic acid were also evaluated in a modification of the in vivo test procedure described above. In the modified test procedure, treatment with rapamycin or rapamycin plus mycophenolic acid were stopped on day 14, as above, but the animals were not sacrificed immediately. Intimal thickening was observed when the animals were sacrificed 1, 2, 4 weeks, and 44 days after treatment had been stopped. Microscopic analysis showed that endothelium regeneration had not occurred during the two week treatment period. For example, 44 days after undergoing balloon catheterization procedure of the carotid artery, untreated injured control rats had an intima percent (±S.E.) of 62.85±3.63, and rats treated with rapamycin+mycophenolic acid (1.5/40 mg/kg) on postoperative days 0–13 had an intima percent (±S.E.) of 50.39±2.58. Better results were not obtained when the same regimen was administered on days 0–30 (intima percent (±S.E.) of 53.55±2.85). Following cessation of treatment with rapamycin or rapamycin plus mycophenolic acid intimal proliferation, that was previously suppressed, was able to occur. These results are consistent with the results shown in the table above, in which treatment for 2 days with rapamycin followed by 12 days of no treatment inhibited intimal thickening to a lesser degree than treatment with rapamycin for 14 days. These results are expected, as in the absence on an integral endothelial layer, the intimal smooth muscle cells will proliferate. It has been shown that intimal smooth muscle cell growth does not have an inhibitory effect on normal endothelial regeneration, and that intimal smooth muscle cell proliferation ceases when the endothelial layer is established. [Reidy, M., *Lab. Invest.* 59:36 (1988); Chevru, A., *Surg. Gynecol. Obstet.* 171:443 (1990); Fishman, J., *Lab. Invest.* 32:339 (1975); Haudenschild, C., *Lab. Invest.* 41:407 (1979)]. As such, treatment with rapamycin or rapamycin in combination with mycophenolic acid should be employed so long as the beneficial effect is seen. As the degree of restenosis can be monitored by angiographic and sonographic techniques, the dosage necessary to sustain the opened vessels can be adjusted.

To evaluate the ability of rapamycin and rapamycin plus mycophenolic acid to prevent restenosis following an angioplasty procedure, rapamycin was evaluated in the same in vivo standard pharmacological test procedure for restenosis that was described above, except that treatment with rapamycin began three days before (day –3) the angioplasty procedure was performed. The following table shows the results obtained on day 14 following balloon catheterization of the carotid artery on day 0. Results for treatment from day 3 to 13 are also provided.

EFFECT OF RAPAMYCIN ON INTIMAL THICKENING IN INJURED CAROTID ARTERIES (DAY 14)

Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control			0.00 ± 0.00
Untreated Injured Control			44.51 ± 5.03
Rapamycin	1.5 mg/kg	–3–13*	9.85 ± 1.15
Rapamycin	1.5 mg/kg	–3–3	30.7 ± 6.67
Rapamycin	1.5 mg/kg	–3–0	37.31 ± 4.33
Rapamycin	1.5 mg/kg	3–13	44.38 ± 5.49

*Treatment from three days pre-balloon catheterization to day 13 days post-catheterization.

The results in the table above show that rapamycin prevented the development of restenosis following a balloon angioplasty procedure of the carotid artery, when rapamycin was administered from three days pre-angioplasty until day 13. Treatment from day minus 3 until day 3 or day 0 afforded a lesser degree of prevention, and treatment from day 3 to day 13 did not prevent restenosis.

The effect of rapamycin plus mycophenolic acid (MPA) was also evaluated in the angioplasty standard pharmacological test procedure. The table below shows the results obtained where rats underwent a balloon catheterization procedure of the carotid artery on day 0, and were sacrificed and examined morphometrically on day 44. The treatment regimen is described in the table.

EFFECT OF RAPAMYCIN + MPA ON INTIMAL THICKENING IN INJURED CAROTID ARTERIES (DAY 44)

Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control			0.00 ± 0.00
Untreated Injured Control			62.85 ± 3.63
Rapamycin + MPA	40/1.5 mg/kg	0–13	50.39 ± 2.58
Rapamycin + MPA	40/1.5 mg/kg	0–30	53.55 ± 2.85
Rapamycin + MPA	40/1.5 mg/kg	–3–13	18.76 ± 10.6

These results show that treatment with rapamycin and mycophenolic acid from day minus 3 to day 13 did effec-

tively prevent restenosis at day 44, whereas the regimens which did not include drug administration before the angioplasty procedure did not effectively prevent restenosis at day 44.

Similar results were obtained when rat thoracic aortas were subjected to a balloon catheterization procedure, as described above, on day 0. The rats were either sacrificed and examined on day 14 or on day 44. The results obtained with rapamycin and rapamycin plus mycophenolic acid (MPA) are shown in the table below.

EFFECT OF RAPAMYCIN AND RAPAMYCIN + MPA ON INTIMAL THICKENING IN INJURED THORACIC AORTAS

Group	Dose	Treatment Days	Intima Percent ± S.E.
Day 14 results			
Uninjured Control			0.00 ± 0.00
Untreated Injured Control			15.52 ± 2.99
Rapamycin + MPA	40/1.5 mg/kg	–3–13	0.00 ± 0.00
Day 44 Results			
Uninjured Control			0.00 ± 0.00
Untreated Injured Control			28.76 ± 6.52
Rapamycin	1.5 mg/kg	–3–13	0.00 ± 0.00
Rapamycin + MPA	40/1.5 mg/kg	–3–13	8.76 ± 3.34

The results in the table above show that treatment with rapamycin from 3 days preoperatively until 13 days postoperatively completely prevented the development of restenosis 44 days after a balloon catheterization of the thoracic aorta. Using the same treatment regimen, rapamycin plus mycophenolic acid completely prevented restenosis 14 days after balloon catheterization and significantly prevented restenosis 44 days following balloon catheterization.

Similarly, day minus 3 to day 13 treatment with rapamycin plus mycophenolic acid completely prevented restenosis 14 days after balloon catheterizaton of the abdominal aortas in rats. These results are shown in the table below.

EFFECT OF RAPAMYCIN + MPA ON INTIMAL THICKENING IN INJURED ABDOMINAL AORTAS (DAY 14)

Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control			0.00 ± 0.00
Untreated Injured Control			10.17 ± 2.42
Rapamycin + MPA	40/1.5 mg/kg	–3–13	0.00 ± 0.00

The results in the tables above show that rapamycin, alone or in combination with mycophenolic acid, is useful in preventing restenosis following invasive procedures that disrupt the vascular endothelial lining, such as percutaneous transluminal coronary angioplasty, vascular catheterization, vascular scraping, vascular surgery, or laser treatment procedures. These data also show that the administration of rapamycin, alone or in combination with mycophenolic acid, from 3 days pre-catheterization to 13 days post-catheterization, allowed the endothelium to heal, while preventing intimal smooth muscle cell proliferation. That intimal proliferation did not occur 31 days after administration with rapamycin, alone or in combination with mycophenolic acid, had been stopped, demonstrates that the endothelial layer had regenerated, as intimal proliferation stops after the reestablishment of the endothelial layer. The reestablishment of an intact endothelial layer was confirmed by microscopic examination of the previously catheterized arteries after removal at 44 days.

From the data above, it is particularly preferred that treatment begin with rapamycin or rapamycin plus mycophenolic acid before the procedure is performed, and that treatment should continue after the procedure has been performed. The length of treatment necessary to prevent restenosis will vary from patient to patient. For percutaneous transluminal angioplasty procedures, it is preferred that treatment be administered from 3 or more days before the procedure and continuing for 8 or more days after the procedure. It is more preferred that administration will be for 3 or more days before the angioplasty procedure and continuing for 13 or more days after the procedure. The same administration protocol is applicable when rapamycin, alone or in combination with mycophenolic acid, is used to prevent restenosis following vascular catheterization, vascular scraping, vascular surgery, or laser treatment procedures.

When rapamycin is employed alone or in combination with mycophenolic acid in the prevention or treatment of hyperproliferative vascular disease, it can be formulated neat or with a pharmaceutical carrier to a mammal in need thereof. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example,

intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compound can also be administered orally either in liquid or solid composition form.

Rapamycin, alone or in combination with mycophenolic acid, may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. Rapamycin, alone or in combination with mycophenolic acid, may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermiable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Rapamycin, alone or in combination with mycophenolic acid can be administered intravascularly or via a vascular stent impregnated with rapamycin, alone or in combination with mycophenolic acid, during balloon catheterization to provide localized effects immediately following injury.

Rapamycin, alone or in combination with mycophenolic acid, may be administered topically as a solution, cream, or lotion by formulation with pharmaceutically acceptable vehicles containing 0.1–5 percent, preferably 2%, of active compound.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedures, projected daily intravenous dosages of rapamycin, when administered as the sole active compound or in combination with mycophenolic acid, would be 0.001–25 mg/kg, preferably between 0.005–10 mg/kg, and more preferably between 0.01–5 mg/kg. Projected daily oral dosages of rapamycin, when administered as the sole active compound or in combination with mycophenolic acid, would be 0.005–50 mg/kg, preferably between 0.01–25 mg/kg, and more preferably between 0.05–10 mg/kg. Projected daily intravenous dosages of mycophenolic acid, when used in combination with rapamycin, would be 0.5–75 mg/kg and preferably between 5–50 mg/kg. Projected daily oral dosages of mycophenolic acid, when used in combination with rapamycin, would be 1–75 mg/kg and preferably between 10–50 mg/kg.

Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, intravascular, intranasal, intrabronchial, transdermal, or rectal administration will be determined by the administering physician based on experience with the individual subject treated. In general, rapamycin is most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects, and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

What is claimed is:

1. A method of preventing restenosis in a mammal resulting from said mammal undergoing a vascular catheterization, vascular scraping, vascular surgery, or laser treatment procedure which comprises administering an antirestenosis effective amount of rapamycin to said mammal orally, parenterally intravascularly, intranasally, intrabronchially, transdermally, rectally, or via a vascular stent impregnated with rapamycin.

2. The method according to claim 1, wherein the administration of the rapamycin is initiated before the mammal undergoes the procedure.

3. The method according to claim 2, wherein the rapamycin is administered for 3 or more days before the mammal undergoes the procedure and said administration continues for 8 or more days following the procedure.

4. The method according to claim 3, wherein the rapamycin is administered for 13 or more days following the procedure.

* * * * *

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Angela Kyle

DATE April 19, 1996

AHP-9897-6-N5
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: R.E. Morris
C.R. Gregory

Serial No.: 08/452,051 **Examiner:** Witz

Filed: May 26, 1995 **Group:** 1808

For: Method of Treating Hyperproliferative Vascular Disease

DOCKETED

Assistant Commissioner for Patents
Washington, DC 20231

DUE DATE

BY cad 4/25/96

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American Home Products Corporation has reviewed the evidentiary documents submitted to establish its ownership of the patents and patent applications referred to in this Terminal Disclaimer and certifies that to the best of its knowledge and belief, title is in American Home Products Corporation.

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for American Home Products Corporation
Reg. No. 35,288

Dated: April 19, 1996
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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,563,146	183	830	----	08/452,051	10/08/96	05/26/95	04	NO	PAID

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PTOL-439 (REV. 11-97)

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Instructions for Use

CYPHER™ Sirolimus-eluting Coronary Stent on RAPTOR™ Over-the-Wire Delivery System

and

CYPHER™ Sirolimus-eluting Coronary Stent on RAPTORRAIL® Rapid Exchange Delivery System

Table of Contents

1. Product Description

The **CYPHER™** Sirolimus-eluting Coronary Stent (**CYPHER** Stent) is a combination product comprised of two regulated components: a device (a stent system) and a drug product (a formulation of sirolimus in a polymer coating).

1.1. Device Component Description

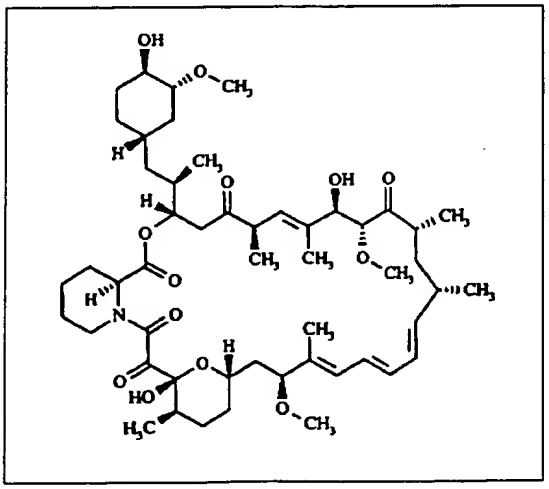
The device component consists of a stent mounted onto a stent delivery system (SDS). The physical characteristics of the device component are shown in Table 1-1.

Table 1-1: Device Component Description

	CYPHER™ Sirolimus-eluting Coronary Stent on RAPTOR™ Over-the-Wire (OTW) Stent Delivery System	**CYPHER™ Sirolimus-eluting Coronary Stent on RAPTORRAIL® Rapid Exchange (RX) Stent Delivery System**
Available Stent Lengths, unexpanded (mm):	8, 13, 18, 23, 28, 33	8, 13, 18, 23, 28, 33
Available Stent Diameters (mm):	2.50, 2.75, 3.00, 3.50	2.50, 2.75, 3.00, 3.50
Stent Material:	Electropolished stainless steel (316L), laser-cut from seamless tubing in a sinusoidal pattern coated with a polymer and sirolimus mixture.	
Stent Geometry:	Six circumferential cells (2.50 – 3.00 mm stents) or Seven circumferential cells (3.50 mm stents)	
Nominal Stent Foreshortening:	≤ 1 mm	
Delivery System Usable Length:	145 cm	137 cm
Delivery System Y-Adapter Ports:	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen – designed for guidewire ≤ 0.014" (0.36 mm).)	Single access port to the inflation lumen. A guidewire exit port is located at 28 cm from the tip. Designed for guidewire ≤ 0.014" (0.36 mm).
Stent Delivery Balloon:	Single-layer nylon, nominally 2 mm longer than stent. Mounted stent length and location is defined by 2 platinum-iridium radiopaque marker bands.	
Balloon Inflation Pressure:	Nominal pressure: 11 atm (1115 kPa) Rated burst pressure: 16 atm (1621 kPa)	
Guiding Catheter Inner Diameter:	≥ 0.067" (1.7 mm)	≥ 0.056" (1.4 mm) for 2.50 – 3.00 mm ≥ 0.067" (1.7 mm) for 3.50 mm
Catheter Shaft Outer Diameter:	3.3F (1.10 mm) proximally, 2.7F (0.90 mm) distally.	2.3F (0.75 mm) proximally; 2.6F (0.85 mm) distally (Ø up to 3.00 mm); 2.9F (0.95 mm) distally (Ø > 3.00 mm).

1.2. Drug Component Description

The active ingredient in the **CYPHER** Sirolimus-eluting Coronary Stent is sirolimus (also known as rapamycin). Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula of sirolimus is shown below:



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile. Please refer to Table 1-2 for the nominal dosages of sirolimus on the **CYPHER** Sirolimus-eluting Coronary Stents.

The inactive ingredients in the **CYPHER** Sirolimus-eluting Coronary Stent contain parylene C and the following two non-erodible polymers: polyethylene-co-vinyl acetate (PEVA) and poly n-butyl methacrylate (PBMA). A combination of the two polymers mixed with sirolimus (67%/33%) makes up the basecoat formulation which is applied to a parylene C treated stent. A drug-free topcoat of PBMA polymer is applied to the stent surface to control the release kinetics of sirolimus. The drug/polymer coating is adhered to the entire surface (i.e., luminal and abluminal) of the stent. The structural formulae of the polymer subunits are shown below:

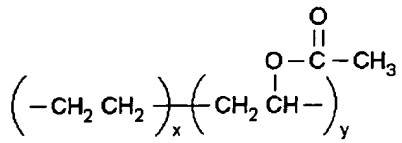
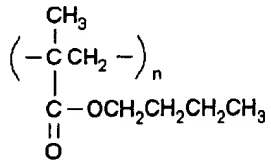
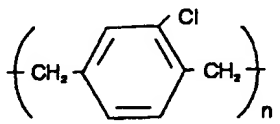
PEVA	PBMA	Parylene C
		

Table 1-2: CYPHER Sirolimus-eluting Coronary Stent System
Product Matrix & Nominal Sirolimus Dosages

Product Code		Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Sirolimus Content (µg)	Product Code		Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Sirolimus Content (µg)
OTW	RX				OTW	RX			
CWS08250	CXS08250	2.50	8	71	CWS23250	CXS23250	2.50	23	190
CWS08275	CXS08275	2.75	8	71	CWS23275	CXS23275	2.75	23	190
CWS08300	CXS08300	3.00	8	71	CWS23300	CXS23300	3.00	23	190
CWS08350	CXS08350	3.50	8	83	CWS23350	CXS23350	3.50	23	221
CWS13250	CXS13250	2.50	13	111	CWS28250	CXS28250	2.50	28	229
CWS13275	CXS13275	2.75	13	111	CWS28275	CXS28275	2.75	28	229
CWS13300	CXS13300	3.00	13	111	CWS28300	CXS28300	3.00	28	229
CWS13350	CXS13350	3.50	13	129	CWS28350	CXS28350	3.50	28	268
CWS18250	CXS18250	2.50	18	150	CWS33250	CXS33250	2.50	33	268
CWS18275	CXS18275	2.75	18	150	CWS33275	CXS33275	2.75	33	268
CWS18300	CXS18300	3.00	18	150	CWS33300	CXS33300	3.00	33	268
CWS18350	CXS18350	3.50	18	175	CWS33350	CXS33350	3.50	33	314

2. Indications

The **CYPHER** Sirolimus-eluting Coronary Stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete *de novo* lesions of length ≤ 30 mm in native coronary arteries with a reference vessel diameter of ≥ 2.5 to ≤ 3.5 mm.

Long-term outcome (beyond 12 months) for this permanent implant is unknown at present.

3. Contraindications

Use of the **CYPHER** Sirolimus-eluting Coronary Stent is contraindicated in the following patient types:

- Patients with a hypersensitivity to sirolimus or its derivatives.
- Patients with a known hypersensitivity to polymethacrylates or polyolefin copolymers.

Coronary artery stenting is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon.

4. Warnings

- Please ensure that the inner package has not been opened or damaged as this may indicate the sterile barrier has been breached.
- The use of this device carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events.
- Patients with a known hypersensitivity to 316L stainless steel may suffer an allergic reaction to this implant.

5. Precautions

5.1. General Precautions

- Only physicians who have received adequate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent stent blockage may require repeat dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of endothelialized stents is not well characterized.
- To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.
- Do not use Ethiodol or Lipiodol contrast media.[1]
- Do not expose the delivery system to organic solvents, such as alcohol, or detergents.

5.2. Use of Multiple Stents

The extent of the patient's exposure to drug and polymer is directly related to the number of stents implanted. Use of more than two **CYPHER** Stents has not received adequate clinical evaluation. Use of more than two **CYPHER** Stents will result in the patient receiving larger amounts of drug and polymer than the experience reflected in the clinical studies.

5.3. Brachytherapy

The safety and effectiveness of the **CYPHER** Stent in patients with prior brachytherapy of the target lesion have not been established. The safety and effectiveness of use of brachytherapy to treat in-stent restenosis in a **CYPHER** Stent have not been established. Both vascular brachytherapy and the **CYPHER** Stent alter arterial remodeling. The synergy between these two treatments has not been determined.

[1] Ethiodol and Lipiodol are trademarks of Guerbet, S.A.

5.4. Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with **CYPHER** Stent implantation have not been established.

5.5. Use in Special Populations

5.5.1. Pregnancy: Pregnancy Category C. See **Drug Information – 6.6 Pregnancy.**
There are no adequate and well controlled studies in pregnant women. Effective contraception should be initiated before implanting a **CYPHER** Stent and for 12 weeks after implantation. The **CYPHER** Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

5.5.2. Use during lactation: See **Drug Information – 6.7 Lactation.** A decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

5.5.3. Pediatric use: The safety and efficacy of the **CYPHER** Stent in pediatric patients below the age of 18 years have not been established.

5.5.4. Geriatric use: Clinical studies of the **CYPHER** Stent did not find that patients age 65 years and over differed with regard to safety and efficacy compared to younger patients.

5.6. Lesion/Vessel Characteristics

The safety and effectiveness of the **CYPHER** Stent have not been established in the following patient populations:

- Patients with unresolved vessel thrombus at the lesion site.
- Patients with coronary artery reference vessel diameter < 2.5 mm or > 3.5 mm.
- Patients with lesions located in the left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with diffuse disease or poor overflow distal to the identified lesions.
- Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
- Patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.

5.7. Drug Interactions

Several drugs are known to affect the metabolism of sirolimus, and other drug interactions may be inferred from known metabolic effects. Sirolimus is known to be a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. See **Drug Information – 6.4 Drug Interactions Following Oral Administration of Sirolimus** for more specific information.

Consideration should be given to the potential for drug interaction when deciding to place a **CYPHER** Stent in a patient who is taking a drug that could interact with sirolimus, or when deciding to initiate therapy with such a drug in a patient who had recently received a **CYPHER** Stent. The effect of drug interactions on the safety or efficacy of the **CYPHER** Stent has not been determined.

5.8. Coronary Artery Surgery – Effect on Anastomoses

There have been rare reports of bronchial anastomotic dehiscence of transplant anastomoses in lung transplant patients who were receiving oral sirolimus therapy. In a vessel that has recently been implanted with a **CYPHER** Stent, the sirolimus concentrations are expected to be several fold higher than systemic sirolimus concentrations. Therefore, consideration should be given to the possibility that the presence of a **CYPHER** Stent may compromise the healing of coronary artery vascular anastomoses. No such event was observed in the very limited experience from clinical trials.

5.9. Immune Suppression Potential

Sirolimus, the active ingredient of the **CYPHER** Stent, is an immunosuppressive agent that is also available in oral formulations. The mean peak systemic blood concentration of sirolimus following placement of up to two **CYPHER** Stents (1.05 ng/ml) is substantially lower than the therapeutic concentrations usually obtained when sirolimus oral formulations are used as prophylaxis for renal transplant rejection (see **Drug Information – Pharmacokinetics** (6.2)). In clinical studies of **CYPHER** Stents when used according to its intended use, there were no reports of immune suppression. However, for patients who receive several **CYPHER** Stents simultaneously, it may be possible for systemic concentrations of sirolimus to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiently or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. This possibility should be considered for such patients, particularly if they are also taking oral sirolimus (or rapamycin), other immunosuppressive agents, or are otherwise at risk for immune suppression.

5.10. Lipid Elevation Potential

The use of oral sirolimus in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, the systemic sirolimus concentrations from the **CYPHER** Stent are expected to be lower than the concentrations usually obtained in transplant patients, but the magnitude and duration of any effect of those concentrations on lipids is not known.

5.11. Magnetic Resonance Imaging (MRI) – Stent Migration

An MRI scan should not be performed on a patient after stent implantation until there is adequate neointimal investment of the stent because of a potential for stent migration. For a conventional uncoated 316L stainless steel stent this period is usually considered to be eight weeks. Because of the reduced neointimal formation associated with the **CYPHER** Stent, the period of vulnerability may be longer, but there is currently insufficient information to provide a specific recommendation.

5.12. Stent Handling Precautions

- **For single use only.** Do not resterilize or reuse this device. Note the "Use By" date on the product label.
- **Do not remove the stent from the delivery balloon – removal may damage the stent and/or lead to stent embolization.** The stent system is intended to perform as a system.
- **Do not induce a vacuum on the delivery system prior to reaching the target lesion.**
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the large-bore rotating hemostatic valve and guiding catheter hub.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may loosen the stent from the delivery system balloon and cause dislodgment.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.

5.13. Stent Placement Precautions

- **Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in Section 12 – Operator's Manual.**
- Guiding catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Product Description – 1.1 Device Component Description**).
- Do not induce a negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon.
- Although the stent delivery balloon catheter is strong enough to expand the stent without rupture, a circumferential tear of the carrier balloon distal to the stent and prior to complete expansion of the stent could cause the balloon to become tethered to the stent, requiring surgical removal. In case of rupture of the balloon, it should be withdrawn and, if necessary, a new balloon catheter exchanged over the guidewire to complete the expansion of the stent.

- Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (CABG, further dilatation, placement of additional stents, or other intervention).
- Do not expand the stent if it is not properly positioned in the vessel. (See **Precautions – 5.14 Stent/System Removal Precautions.**)
- Placement of the stent has the potential to compromise side branch patency.
- Balloon pressures should be monitored during inflation. **Do not exceed rated burst pressure as indicated on the product label.** (See **Inflation Pressure Recommendations** in Table 12-1.) Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- **Do not attempt to pull an unexpanded stent back through the guiding catheter, as dislodgment of the stent from the balloon may occur. Remove as a single unit per instructions in Precautions – 5.14 Stent/System Removal Precautions.**
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.

5.14. Stent/System Removal Precautions

Should **unusual resistance** be felt **at any time** during either lesion access or removal of the stent delivery system before stent implantation, the entire system **should be removed as a single unit.**

When removing the delivery system as a single unit:

- Do not retract the delivery system into the guiding catheter.
- Advance the guidewire into the coronary anatomy as far distally as safely possible.
- Tighten the rotating hemostatic valve to secure the stent delivery system to the guiding catheter; then remove the guiding catheter and stent delivery system as a **single unit.**

Failure to follow these steps or applying excessive force to the stent delivery system can potentially result in loss or damage to the stent or stent delivery system.

If it is necessary to retain the guidewire in position for subsequent artery/lesion access, leave the guidewire in place and remove all other system components.

5.15. Post Implantation Precautions

- Great care must be exercised **when crossing a newly deployed stent** with an intravascular ultrasound (IVUS) catheter, a coronary guidewire or balloon catheter to avoid disrupting the stent geometry.
- Do not perform a **magnetic resonance imaging** (MRI) scan on a patient after stent implantation until there is adequate neointimal investment of the stent (see **Precautions – 5.11 Magnetic Resonance Imaging (MRI) – Stent Migration**). The stent may cause artifacts in MRI scans due to distortion of the magnetic field.

6. Drug Information

6.1. Mechanism of Action

The mechanism (or mechanisms) by which a **CYPHER** Stent affects neointima production as seen in clinical studies has not been established. It is known that sirolimus inhibits T-lymphocyte activation and smooth muscle and endothelial cell proliferation in response to cytokine and growth factor stimulation. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The sirolimus-FKBP-12 complex binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), leading to inhibition of cell cycle progression from the G_1 to the S phase.

6.2. Pharmacokinetics of the CYPHER Sirolimus-eluting Coronary Stent

The pharmacokinetics of sirolimus as delivered by the **CYPHER** Sirolimus-eluting Coronary Stent has been determined in patients with coronary artery disease after implantation of 1 (n=10) or 2 (n=9) **CYPHER** Stents. The parameters determined from patients receiving 1 and 2 **CYPHER** stents are provided in Table 6-1.

Table 6-1: Whole Sirolimus Pharmacokinetic Parameters in Patients after Implantation of CYPHER Sirolimus-eluting Coronary Stents

Number of Stents	Statistic	Dose (µg)	t_{max} (h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	AUC (ng•h/ml)	CL (ml/h/kg)
1 (n=10)	Mean	161	3.90	0.57	206	127	17.7
	SD	15	2.38	0.12	92	51	7.5
	%CV	9.09	61.0	20.5	44.8	40.3	42.2
	Range	149-178	1-6	0.43-0.77	111-354	58-225	6.22-29.2
2 (n=9)	Mean	315	3.24	1.05	220	227	17.1
	SD	25	3.59	0.39	106	58	5.3
	%CV	7.84	111	37.4	48.3	25.7	31.2
	Range	299-355	1.05-12.2	0.51-1.66	131-486	149-307	9.31-24.5

t_{max} = time peak concentration occurs; C_{max} = peak blood concentration; $t_{1/2}$=terminal-phase half-life; AUC=area under the concentration-time curve; CL=total blood clearance

The results in Table 6-1 show that C_{max} and AUC were closely dose-proportional over a 2-fold range in doses. The blood levels after stent implantation were 10 to 20 fold lower than what was observed after oral administration of sirolimus in either healthy volunteers or transplanted patients. The mean ± SD sirolimus terminal half-life ($t_{1/2}$) after stent implantation for the combined groups (n = 19) was 213 ± 97 h. By comparison, the mean ± SD sirolimus $t_{1/2}$ values after single dose administration of sirolimus by oral solution in healthy subjects (n = 305) and renal transplant patients (n = 81) were 72.9 ± 19.3 h and 58.2 ± 19.2 h, respectively. The apparent discrepancy in half-lives after stent implantation and oral administration is due to the fact that the decline in terminal sirolimus concentrations reflects the release of sirolimus from the stent and not elimination of sirolimus from the body.

6.3 Pharmacokinetics Following Oral Administration of Sirolimus

Sirolimus pharmacokinetic activity has been determined following oral administration in healthy subjects, pediatric dialysis patients, hepatically-impaired patients, and renal transplant patients. Table 6-2 provides a summary of the descriptive statistics for the maximum whole blood sirolimus pharmacokinetic exposure, based on t_{max}, C_{max} and AUC.

Table 6-2: Pharmacokinetic Parameters (mean ± SD) in Healthy Subjects, Renal Transplant Patients and Patients with Hepatic Impairment Following Oral Administration of Sirolimus

Patient Status(n)	Dose	t_{max} (hours)	C_{max}(ng/ml)	AUC (ng•h/ml)
Healthy (n=18)	15 mg single dose oral solution	0.82 ± 0.17	78.2 ± 18.3	970 ± 272
Renal Transplant (n=19)	2 mg/day multiple dose oral solution	3.01 ± 2.4	12.2 ± 6.2	158 ± 70
Renal Transplant (n=23)	5 mg/day multiple dose oral solution	1.84 ± 1.3	37.4 ± 21	396 ± 193
Renal Transplant (n=13)	2 mg/day multiple dose tablets	3.46 ± 2.4	15.0 ± 4.9	230 ± 67
Hepatic Impairment (n=18)	15 mg single dose oral solution	0.84 ± 0.17	77.9 ± 23.1	1567 ± 616

6.3.1. Distribution

The mean (±SD) blood to plasma ratio of sirolimus was 36 (±18) in stable renal allograft patients, indicating that sirolimus is extensively partitioned into formed blood elements. Sirolimus is extensively bound (approximately 92%) to human plasma proteins. In man the binding of sirolimus was shown mainly to be associated with serum albumin (97%), alpha-1 acid glycoprotein and lipoproteins.

6.3.2. Metabolism

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven major metabolites, including sirolimus, demethyl, and hydroxydemethyl are identifiable in blood. Some of these metabolites are also detectable in plasma, fecal and urine samples. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

6.3.3. Special Populations

Hepatic impairment: Sirolimus (15 mg) was administered as a single oral dose to 18 subjects with normal hepatic function and 18 patients with Child-Pugh classification A or B hepatic impairment, in which hepatic impairment was primary and not related to an underlying systemic disease. Compared with the values in the normal hepatic group, the hepatic impairment had higher mean AUC (61%) and $t_{1/2}$ (43%) and had lower mean clearance values (33%). The mean $t_{1/2}$ increased from 79 ± 12 hours in subjects with normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function. However, hepatic diseases with varying etiologies may show different and the pharmacokinetics of sirolimus in patients with severe hepatic dysfunction is unknown.

Renal impairment: The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites.

Demographics: After oral administration of sirolimus there was no effect of gender, race and age (> 65 years) on the pharmacokinetics of sirolimus.

6.4 Drug Interactions Following Oral Administration of Sirolimus

Drug interaction studies have not been conducted with the **CYPHER** Sirolimus-eluting Coronary Stent. Sirolimus is extensively metabolized by cyctochrome P450 3A4 (CYP3A4) in the gut wall and liver and undergoes efflux from enterocytes of the small intestine by P-glycoprotein (P-gp). Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Inhibitors of CYP3A4 and P-gp may increase sirolimus levels, while inducers of CYP3A4 and P-gp may decrease sirolimus levels. The pharmacokinetic interaction between orally administered sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

6.4.1. Ketoconazole

Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of a sirolimus oral formulation, as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose sirolimus did not affect steady-state 12-hour plasma ketoconazole concentrations. It is recommended that sirolimus oral solution and oral tablets should not be administered with ketoconazole.

6.4.2. Rifampin

Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of sirolimus, greatly increased sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decreases in AUC and C_{max} of about 82% and 71%, respectively. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

6.4.3. Diltiazem

The simultaneous oral administration of 10 mg of a sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem.

6.4.4. Cyclosporine

Single-dose pharmacokinetic interactions between cyclosporine and sirolimus were investigated for two sirolimus oral formulations in studies using 24 healthy volunteers. Compared to results obtained when oral sirolimus was administered alone, the oral administration of 10 mg sirolimus 4 hours after a single dose of 300 mg cyclosporine soft gelatin capsules increased mean sirolimus AUC by 33% to 80% and increased mean sirolimus C_{max} by 33% to 58%, depending on the sirolimus formulation. The half-life of sirolimus was not significantly affected. The cyclosporine mean AUC and mean C_{max} were not significantly affected.

6.4.5. Drugs which may be coadministered without dose adjustment
Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below in conjunction with orally administered sirolimus. Sirolimus and these drugs may be coadministered without dose adjustments.

- Acyclovir
- Digoxin
- Glyburide
- Nifedipine
- Norgestrel/ethinyl estradiol
- Prednisolone
- Sulfamethoxazole/trimethoprim

6.4.6. Other drug interactions
Drugs that may increase sirolimus blood concentrations include:

- **Calcium channel blockers:** nicardipine, verapamil.
- **Antifungal agents:** clotrimazole, fluconazole, itraconazole.
- **Macrolide antibiotics:** clarithromycin, erythromycin, troleandomycin.
- **Gastrointestinal prokinetic agents:** cisapride, metoclopramide.
- **Other drugs:** bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

Drugs that may decrease sirolimus levels include:

- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin.
- **Antibiotics:** rifabutin, rifapentine.

These lists are not all inclusive.

Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with implantation of **CYPHER** Stents.

6.4.7. **Grapefruit juice:** Grapefruit juice reduces CYP3A4-mediated metabolism of sirolimus.

6.4.8. **Herbal Preparations:** St. John's Wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Because sirolimus is a substrate for both cytochrome CYP3A4 and P-glycoprotein, there is the potential that the use of St. John's Wort in patients receiving **CYPHER** Stents could result in reduced sirolimus levels.

6.4.9. Vaccination
Immunosuppressants may affect response to vaccination. Therefore, for some period after receiving a **CYPHER** Stent, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

6.4.10. Drug-laboratory test interactions
There are no studies on the interactions of sirolimus in commonly employed clinical laboratory tests.

6.5. Mutagenesis, Carcinogenicity and Reproductive Toxicology
The genotoxicity, carcinogenicity, and reproductive toxicity of **CYPHER** Stents have not been evaluated. However, the genotoxicity, carcinogenicity, and reproductive toxicity of sirolimus have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*.

Sirolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the *in vivo* mouse micronucleus assay.

Carcinogenicity studies in mouse showed hepatocellular adenoma and carcinoma at dosages of 1, 3 and 6 mg/kg/day orally (approximately 15 to 94 times the dosage provided by a stent coated with 314 µg sirolimus, adjusted for body surface area). In the 104-week rat study at dosage of 0.2 mg/kg/day (approximately 6 times the dosage provided by a stent coated with 314 µg sirolimus adjusted for body surface area), there was a significant increase in the incidence of testicular adenoma.

There was no effect on fertility in female rats following the administration of sirolimus at dosages up to 0.5 mg/kg/day (approximately 15 times the dosage provided by a stent coated with 314 µg sirolimus adjusted for body surface area). In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg/day (approximately 60 times the dosage provided by a stent coated with 314 µg sirolimus adjusted for body surface area). Reduction in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats following dosages of $\geq$ 0.65 mg/kg/day (approximately 20 times the dosage provided by a stent coated with 314 µg sirolimus adjusted for body surface area).

6.6. Pregnancy
Pregnancy Category C: There are no adequate and well controlled studies in pregnant women of sirolimus or **CYPHER** Stents. Sirolimus was embryo/feto toxic in rats at dosages of $\geq$ 0.1 mg/kg/day (approximately 3 times the dose provided by a stent coated with 314 µg sirolimus adjusted for body surface area). Embryo/feto toxicity was manifested as mortality and reduced fetal weights, with associated delays in skeletal ossification. No teratogenic effect of sirolimus was evident. There was no effect of sirolimus on rabbit development at the maternally toxic dosage of 0.05 mg/kg/day (approximately 3 times the dose provided by a stent coated with 314 µg sirolimus adjusted for body surface area).

Effective contraception should be initiated before implanting a **CYPHER** Stent and for 12 weeks after implantation. The **CYPHER** Stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus.

6.7. Lactation
Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from sirolimus, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

7. Adverse Events

7.1. Observed Adverse Events

Observed adverse event experience comes from three clinical studies, the SIRIUS trial, the RAVEL trial, and the First-In-Man study. See Section 8 – **Clinical Studies** for more complete descriptions of the study designs and results.

The SIRIUS trial and the RAVEL trial were multi-center, double-blind, randomized clinical trials in patients with symptomatic ischemic coronary artery disease due to *de novo* lesions in native coronary arteries. Patients were randomized to the **CYPHER** Stent (a sirolimus-eluting **BX VELOCITY™** Stent) or to a Control stent (**BX VELOCITY**, an uncoated 316L stainless steel stent). Eligibility was based on visual estimates of vessel diameter and lesion length. Following treatment, patients were treated with aspirin indefinitely and either clopidogrel or ticlopidine for 2 or 3 months, depending on the trial. Evaluations included clinical and angiographic outcomes. The First-In-Man study was a small, non-randomized, two-center study that used the **CYPHER** Stent in 30 of its 45 patients. Major study characteristics are summarized in Table 7-1. Principal adverse events are shown in Table 7-2.

Table 7-1: Clinical Studies - Major Characteristics

	SIRIUS Trial	RAVEL Trial	First-in-Man Study
Study Type	prospective, randomized	prospective, randomized	non-randomized
Number of Patients	1058 (533 **CYPHER** Stent, 525 Control)	238 (120 **CYPHER** Stent, 118 Control)	45 (30 **CYPHER** Stent, 15 other)
Lesion Criteria	*De novo* lesion in native coronary artery ≥ 2.5 to ≤ 3.5 mm in diameter, lesion 15 to 30 mm in length and coverable with 2 stents	*De novo* lesion in native coronary artery ≥ 2.5 to ≤ 3.5 mm in diameter, lesion coverable by one 18 mm stent	*De novo* lesion in native coronary artery ≥ 3.0 to ≤ 3.5 mm diameter, lesion coverable by one 18 mm stent
Antiplatelet Therapy	Aspirin indefinitely, and ticlopidine or clopidogrel for 3 months	Aspirin indefinitely, and ticlopidine or clopidogrel for 2 months	Aspirin indefinitely, and ticlopidine or clopidogrel for 2 months

Table 7-2: Principal Adverse Events Observed in Clinical Studies In-Hospital and Out-of-Hospital					
	SIRIUS Trial to 360 Days		RAVEL Trial to 720 Days		First-in-Man to 720 Days
	CYPHER Stent (N=533)	Control Stent (N=525)	CYPHER Stent (N=120)	Control Stent (N=118)	CYPHER Stent Stent (N=30)
MACE[1]					
In-Hospital	2.4% (13)	1.5% (8)	2.5% (3)	2.5% (3)	6.7% (2)
Out-of-Hospital	6.0% (32)	21.3% (112)	7.5% (9)	17.8% (21)	3.3% (1)
Death					
In-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	3.3% (1)
Out-of-Hospital	1.1% (6)	0.8% (4)	5.0% (6)	2.5% (3)	0.0% (0)
Myocardial Infarction					
In-Hospital	2.3% (12)	1.5% (8)	2.5% (3)	2.5% (3)	3.3% (1)
Out-of-Hospital	0.8% (4)	1.9% (10)	1.7% (2)	2.5% (3)	0.0% (0)
Q-wave					
In-Hospital	0.4% (2)	0.0% (0)	1.7% (2)	0.8% (1)	0.0% (0)
Out-of-Hospital	0.4% (2)	0.4% (2)	0.0% (0)	0.0% (0)	0.0% (0)
Non Q-wave					
In-Hospital	1.9% (10)	1.5% (8)	0.8% (1)	1.7% (2)	3.3% (1)
Out-of-Hospital	0.4% (2)	1.5% (8)	1.7% (2)	2.5% (3)	0.0% (0)
Emergent CABG					
In-Hospital	0.0% (0)	0.0% (0)	--	--	0.0% (0)
Out-of-Hospital	0.0% (0)	0.0% (0)	--	--	0.0% (0)
Target Lesion Revascularization (TLR)					
In-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	4.7% (25)	20.0% (105)	2.5% (3)	13.6% (16)	3.3% (1)
TVR not Target Lesion					
In-Hospital	0.0% (0)	0.0% (0)	0.8% (1)	0.8% (1)	3.3% (1)
Out-of-Hospital	3.6% (19)	6.7% (35)	0.0% (0)	1.7% (2)	3.3% (1)
Target Vessel Failure[2]					
In-Hospital	2.4% (13)	1.5% (8)	2.5% (3)	2.5% (3)	6.7% (2)
Out-of-Hospital to 270 days[3]	6.6% (35)	19.6% (103)	--	--	--
Out-of-Hospital to 360/720 days	7.5% (40)	23.6% (124)	3.3% (4)	19.5% (27)	3.3% (1)
Stent Thrombosis					
In-Hospital	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	0.2% (1)	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Sub-acute Closure					
In-Hospital	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Out-of-Hospital	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Late Thrombosis					
Out-of-Hospital	0.2% (1)	0.6% (3)	0.0% (0)	0.0% (0)	0.0% (0)
CVA					
In-Hospital	0.2% (1)	0.8% (4)	0.0% (0)	0.0% (0)	3.3% (1)
Out-of-Hospital	0.9% (5)	1.3% (7)	0.8% (1)	0.0% (0)	3.3% (1)

[1] MACE is defined as Death, Q-wave or non Q-wave MI, Emergency CABG, or Target Lesion Revascularization.
[2] Target Vessel Failure is defined as Target Vessel Revascularization, MI or cardiac death that could not be clearly attributed to a vessel other than the target vessel.
[3] TVF at 270 days is the primary endpoint for the SIRIUS study.
Tabulated entries are represented as: percentage (number of patients with event).

In the SIRIUS trial, a subset of patients underwent intravenous ultrasound (IVUS) evaluation of the treated lesion immediately after treatment and as part of a scheduled angiographic evaluation at 8 months. In the RAVEL trial, a subset of patients underwent an IVUS study as part of the follow-up angiographic evaluation at 6 months, but there was no baseline IVUS evaluation. In both studies, patients who received the **CYPHER** Stent had a greater frequency of incomplete stent apposition at follow-up than patients who received the control stent (**BX VELOCITY** Stent, an uncoated 316L stainless steel stent). From the SIRIUS trial, it appeared that in about half of the cases, the incomplete stent apposition had not been observed immediately after stenting (late incomplete stent apposition). Late incomplete stent apposition was not observed in the control group. There were no clinical adverse events that were related to the occurrence of incomplete stent apposition. Frequencies of incomplete stent apposition are shown in Table 7-3.

Table 7-3: Frequency of Incomplete Stent Apposition				
	SIRIUS Trial		RAVEL Trial	
	CYPHER Stent	Control Stent	CYPHER Stent	Control Stent
Incomplete Stent Apposition Rate at Follow-up	18% (18/101)	9% (7/78)	21% (10/41)	4% (2/27)
Changes from Baseline				
Healed	10% (8/80)	5% (3/61)	--	--
Preserved	8% (6/80)	10% (6/61)	--	--
Late Incomplete Stent Apposition	9% (7/80)	0% (0/61)	--	--

7.2. Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with the implantation of a coronary stent in coronary arteries (including those listed in Table 7-2 and Table 7-3):

7.2.1. Potential Adverse Events Associated with Coronary Stent Placement

- Allergic reaction
- Aneurysm
- Arrhythmias
- Cardiac tamponade
- Death
- Dissection
- Drug reactions to antiplatelet agents / anticoagulation agents / contrast media
- Emboli, distal (tissue, air, or thrombotic emboli)
- Embolization, stent
- Emergency CABG
- Failure to deliver the stent to the intended site
- Fever
- Fistulization
- Hemorrhage
- Hypotension/Hypertension
- Incomplete stent apposition
- Infection and pain at the intended site
- Myocardial infarction
- Myocardial ischemia
- Occlusion
- Prolonged angina
- Pseudoaneurysm
- Renal failure
- Restenosis of stented segment (greater than 50% obstruction)
- Rupture of native and bypass graft
- Stent compression
- Stent migration
- Stroke
- Thrombosis (acute, subacute, or late)
- Ventricular fibrillation
- Vessel spasm
- Vessel perforation

7.2.2. Potential Adverse Events Related to Sirolimus (Following Oral Administration):

- Abnormal liver function tests
- Anemia
- Arthralgias
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity, including anaphylactic/anaphylactoid type reactions
- Hypertriglyceridemia (see section 5.10)
- Hypokalemia
- Infections
- Interstitial lung disease
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia

8. Clinical Studies

8.1. Overview of Clinical Studies

The principal safety and efficacy evidence for the **CYPHER** Stent came from three clinical studies, the SIRIUS trial, the RAVEL trial, and the First-In-Man study. All three of these studies evaluated the performance of the **CYPHER** Stent in patients with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and in Table 8-1.

The SIRIUS and RAVEL trials were multi-center, double-blind, randomized clinical trials that compared the **CYPHER** Stent to a Control consisting of an uncoated 316L stainless steel stent (the **BX VELOCITY** Stent). Eligibility was based on visual estimates of vessel diameter and lesion length. Following treatment, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 2 or 3 months, depending on the study. The SIRIUS trial was a large study with a primary clinical endpoint of target vessel failure at 9 months. Angiographic follow-up was scheduled for a majority of patients at 8 months. The RAVEL trial was a smaller study with a primary angiographic endpoint of late loss at 6 months. Clinical follow-up through one year is available for both trials, and follow-up through five years is planned.

The First-in-Man study was a small, non-randomized, initial feasibility study that involved angiographic and clinical follow-up. Its primary value is that it provides the longest available follow-up information, through 2 years.

Table 8-1: Clinical Study Comparison

	SIRIUS Trial	RAVEL Trial	First-in-Man Study
Study Type	Pivotal Study	Supportive Study	Feasibility Study
	Multi-center (N=53), prospective, randomized	Multi-center (N=19), prospective, randomized	Multi-center (N=2) Non-randomized
Number of Patients	1058 (533 **CYPHER** Stent, 525 Control)	238 (120 **CYPHER** Stent, 118 Control)	45 (30 **CYPHER** Stent, 15 other)
Lesion Criteria	*De novo* lesion in native coronary artery ≥ 2.5 to ≤ 3.5 mm in diameter, lesion 15 to 30 mm in length and coverable with 2 stents	*De novo* lesion in native coronary artery ≥ 2.5 to ≤ 3.5 mm in diameter, lesion coverable by one 18 mm stent	*De novo* lesion in native coronary artery ≥ 3.0 to ≤ 3.5 mm diameter, lesion coverable by one 18 mm stent
Device Products Used	**CYPHER** Sirolimus-eluting Coronary Stent on **RAPTOR** Over-the-Wire Stent Delivery System	**CYPHER** Sirolimus-eluting Coronary Stent on **RAPTORRAIL** Rapid Exchange Stent Delivery System	**CYPHER** Sirolimus-eluting Coronary Stent on **RAPTOR** Over-the-Wire Stent Delivery System
Antiplatelet Therapy	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 3 months	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 2 months	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 2 months
Follow-up	8 months angiographic 9 months clinic 1, 3, 6, 12 months and 2, 3, 4 and 5 years telephone F/U	6 months angiographic 1 and 6 month clinic 12 months and 2, 3, 4, and 5 years telephone F/U	Brazil: 4, 12, 24 months angio & IVUS The Netherlands: 6 & 18 months angio & IVUS and 24 months clinical F/U

8.2. SIRIUS Trial (Pivotal Study)

Purpose: The purpose of the trial was to evaluate the safety and effectiveness of the **CYPHER** Stent in reducing target vessel failure in *de novo* native coronary artery lesions.

Conclusions: In selected patients, use of the **CYPHER** Stent significantly reduced the rate of target vessel failure (TVF) at 9 months compared to the Control (**BX VELOCITY** Stent, an uncoated 316L stainless steel stent). Angiographic lesion characteristics at 8 months were also significantly improved.

Design: This was a multi-center, prospective, randomized, double-blind trial conducted at 53 sites in the U.S. The primary efficacy endpoint was pre-specified to be TVF at 9 months, defined as cardiac death, myocardial infarction, or target vessel revascularization. To be eligible, a patient was required to have a *de novo* ischemic lesion of length 15 mm to 30 mm in a native coronary artery of diameter 2.5 mm to 3.5 mm (using visual estimates). Patients could be treated with up to two overlapping stents to cover the lesion.

Patients were randomized with equal probability to receive either the **CYPHER** Stent or the Control. A total of 1101 patients were randomized, and 1058 patients were included in the study results; 533 with **CYPHER** Stent and 525 with Control. A subset of 826 was pre-assigned to have angiographic follow-up at 8 months. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 3 months.

Clinical follow-up through the 12-month (± 2 weeks) endpoint was available on 1027 patients. Angiographic follow-up was obtained on 703 patients. A total of 209 patients had both baseline and follow-up IVUS studies. Clinical follow-up currently is available through one year.

Demography: Baseline characteristics were similar for both treatment arms; factors evaluated included age (mean 62 years), gender (29% female), race (90% Caucasian, 4.3% African American, 3.4% Hispanic, 1.7% Asian, and approximately 0.6% other), diabetes (26%), prior MI (31%), hypertension (68%), hyperlipidemia (74%), ejection fraction (mean 54%), CSS Angina Class (44% III or IV), and IIb/IIIa inhibitor use (60%), LAD (44%), LCX (25%), RCA (31%), reference vessel diameter (mean 2.8 mm), minimum lumen diameter (mean 0.97 mm), percent diameter stenosis (mean 65%), and lesion length (mean 14.4 mm). The overall fraction with a smoking history was 23%, but it was slightly lower in the **CYPHER** Stent arm (20%) than in the control arm (26%); smoking history was not found to be a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical coordinators at the clinical sites. Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated central laboratories. An independent Clinical Events Committee adjudicated clinical events, and the trial was monitored by an independent Data and Safety Monitoring Committee.

Results: In selected patients, elective **CYPHER** Stent placement in native coronary *de novo* lesions resulted in a reduction in the incidence of TVF at 9 months compared to Control (8.8% vs. 21.0%, $p < 0.001$). By follow-up angiography at 8 months, there was significantly lower in-stent late loss (0.17 mm vs. 1.00 mm, $p < 0.001$) and mean in-lesion % diameter stenosis was significantly reduced (23.6% vs. 43.2%, $p < 0.001$). There was no evidence of an edge-effect 5 mm proximal or distal to the stent. Examination by IVUS at 8 months showed that neointimal hyperplasia (NIH) volume was significantly reduced in the **CYPHER** Stent arm (4.4 mm^3 vs. 57.6 mm^3, $p < 0.001$), but there was a higher rate of incomplete stent apposition (18% vs. 9%, $p = 0.13$). There were no clinical events related to the occurrence of incomplete stent apposition. Clinical outcomes through 12 months were consistent with the 9 month outcomes. Twenty-eight percent (28%) of the patients in the **CYPHER** Stent arm of the SIRIUS trial received 2 or more (overlapping) stents. The incidence of major adverse cardiac events in these patients was statistically lower than the patients who received an uncoated stent.

Table 8-2 summarizes the principal effectiveness and safety results of the SIRIUS Trial through 360 days. Figure 8-1 provides the cumulative TVF rates through 360 days.

Table 8-2 SIRIUS Principal Effectiveness and Safety Results (to 360 Days)
All Patients Treated (N=1058)

Effectiveness Measures	CYPHER Stent (N=533 Patients N=533 Lesions)	Control (N=525 Patients N=531 Lesions)	Difference [95% CI]	P-Value
Device Success	97.9% (522/533)	98.7% (524/531)	-0.7% [-2.3, 0.8]	0.477
Procedure Success*	97.4% (519/533)	98.5% (517/525)	-1.1% [-2.8%, 0.6%]	0.281
Post-Procedure MLD (mm)				
In-Stent	2.67 ± 0.40 (528)	2.68 ± 0.42 (526)	0.00 [-0.05, 0.05]	0.985
In-Lesion	2.38 ± 0.45 (530)	2.40 ± 0.46 (526)	-0.01 [-0.07, 0.04]	0.643
Post-Procedure % DS				
In-Stent	5.4% ± 8.2% (529)	6.0% ± 7.9% (526)	-0.6% [-1.6%, 0.4%]	0.229
In-Lesion	16.1% ± 9.7% (530)	16.2% ± 8.5% (526)	-0.1% [-1.2%, 1.0%]	0.792
Eight-Month Follow-up MLD (mm)				
In-Stent	2.50 ± 0.58 (349)	1.69 ± 0.79 (353)	0.82 [0.71, 0.92]	<0.001
In-Lesion	2.15 ± 0.61 (350)	1.60 ± 0.72 (353)	0.55 [0.45, 0.65]	<0.001
Eight-Month Follow-up % DS				
In-Stent	10.4% ± 16.5% (349)	40.1% ± 25.3% (353)	-29.7% [-32.9%, -26.5%]	<0.001
In-Lesion	23.6% ± 16.4% (350)	43.2% ± 22.4% (353)	-19.7% [-22.6%, -16.8%]	<0.001
Eight-Month Late Loss (mm)				
In-Stent	0.17 ± 0.44 (347)	1.00 ± 0.70 (350)	-0.83 [-0.92, -0.74]	<0.001
In-Lesion	0.24 ± 0.47 (348)	0.81 ± 0.67 (350)	-0.57 [-0.66, -0.49]	<0.001
Eight-Month Binary Restenosis				
In-Stent	3.2% (11/349)	35.4% (125/353)	-32.3% [-37.6%, -26.9%]	<0.001
In-Lesion	8.9% (31/350)	36.3% (128/353)	-27.4% [-33.2%, -21.6%]	<0.001
Eight-Month Minimum Lumen Area (mm^2)	5.4 ± 2.1 (101)	3.9 ± 1.9 (75)	1.5 [0.9, 2.1]	<0.001
Eight-Month NIH Volume (mm^3)	4.4 ± 6.5 (51)	57.6 ± 32.7 (45)	-53.2 [-62.5, -43.9]	<0.001
TVF to 9 Months (Primary Endpoint)*	8.8% (47/533)	21.0% (110/525)	-12.1% [-16.4%, -7.9%]	<0.001
Clinical Endpoints to 270 Days				
TLR-Free†	95.8%	83.2%	12.6% [8.5%, 16.7%]	<0.001
TVR-Free†	93.5%	81.1%	12.4% [8.0%, 16.8%]	<0.001
TVF-Free †	91.1%	78.9%	12.2% [7.5%, 16.8%]	<0.001
MACE-Free†	92.8%	81.0%	11.8% [7.4%, 16.3%]	<0.001
Clinical Endpoints to 360 Days				
TLR-Free†	95.0%	79.5%	15.5% [11.4%, 19.7%]	<0.001
TVR-Free†	92.7%	76.9%	15.8% [11.4%, 20.1%]	<0.001
TVF-Free †	90.1%	74.9%	15.2% [10.6%, 19.9%]	<0.001
MACE-Free†	91.7%	77.4%	14.2% [9.8%, 18.7%]	<0.001
Safety Measures				
In-Hospital MACE*	2.4% (13/533)	1.5% (8/525)	0.9% [-0.8%, 2.6%]	0.379
Out-of-Hospital MACE to 270 days*	4.9% (26/533)	17.7% (93/525)	-12.8% [-16.6%, -9.1%]	<0.001
Out-of-Hospital MACE to 360 days*	6.0% (32/533)	21.3% (112/525)	-15.3% [-19.4%, -11.3%]	<0.001
MACE to 270 days*	7.1% (38/533)	18.9% (99/525)	-11.7% [-15.7%, -7.7%]	<0.001
MACE to 360 days*	8.3% (44/533)	22.3% (117/525)	-14.0% [-18.3%, -9.8%]	<0.001
TVF to 270 days (Primary endpoint)*	8.8% (47/533)	21.0% (110/525)	-12.2% [-16.4%, -7.9%]	<0.001
TVF to 360 days*	9.8% (52/533)	24.8% (130/525)	-15.0% [-19.5%, -10.5%]	<0.001
Stent Thrombosis to 30 days	0.2% (1/533)	0.2% (1/525)	0.0% [-0.5%, 0.5%]	1.000
Late Thrombosis to 360 days	0.2% (1/533)	0.6% (3/525)	-0.4% [-1.1%, 0.4%]	0.371
Subacute Closure	0.2% (1/533)	0.0% (0/525)	0.2% [-0.2%, 0.6%]	1.000
Cerebrovascular Accident (CVA) to 360 days	1.1% (6/533)	2.1% (11/525)	-1.0% [-2.5%, 0.5%]	0.231
Major Bleeding Complications	3.6% (19/533)	3.4% (18/525)	0.1% [-2.1%, 2.3%]	1.000
Major (Hemorrhagic) Vascular Complications	1.5% (8/533)	2.3% (12/525)	-0.8% [-2.4%, 0.9%]	0.376
Hematological Dyscrasia to 360 days	0.6% (3/533)	0.8% (4/525)	-0.2% [-1.2%, 0.8%]	0.724

Numbers are % (counts/sample size) or Mean ± SD.
CI = Confidence Interval
Relative Risk = Sirolimus/**BX VELOCITY** Stent
SE = Calculated in SAS[2] software using Mantel-Haenszel Method
CI = RR•exp(±1.96•SE)

All event data were adjudicated by the independent Clinical Events Committee (CEC). All QCA data were assessed by the Angiographic Core Laboratory. All IVUS data were assessed by the IVUS Core Laboratory.

Device Success (Lesion Based) – Achievement of a final residual diameter stenosis of <50% (by QCA) using the assigned device only (if QCA was not available, the visual estimate of diameter stenosis was used).

Procedure Success (Lesion Based) – Achievement of a final diameter stenosis of <50% (by QCA) using any percutaneous method, without the occurrence of death, Q-wave or WHO-defined non Q-wave MI, or repeat revascularization of the target lesion during the hospital stay (if QCA was not available, the visual estimate of diameter stenosis was used).

MLD = Minimum Lumen Diameter

DS = Diameter Stenosis

In-Lesion (Within Segment) – In-lesion measurement was defined as the measurements either within the stented segment or within 5 mm proximal or distal to the stent edges.

In-Stent (Within Stent) – In-stent measurement was defined as the measurement within the stented segment.

NIH = Neointimal Hyperplasia

* Events rates in this table included the WHO definition of non Q-wave MI.

WHO-defined non Q-wave MI – Elevation of post-procedure CK levels to >2 times normal with elevated CKMB in the absence of new pathological Q-waves.

† The following survival estimates are by Kaplan-Meier Methods with standard error estimates by Peto formula:

TLR-Free– No target lesion revascularization.

TVR-Free – No target vessel revascularization.

TVF-Free – No cardiac death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.

MACE-Free – No death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.

Major Adverse Cardiac Events (MACE) – A composite endpoint comprised of death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization.

Target Vessel Failure (TVF) – A composite endpoint comprised of cardiac death, Q-wave or WHO-defined non Q-wave MI, or target vessel revascularization

Stent Thrombosis – A 30-day endpoint including subacute closure or unexplained death or Q-wave MI.

Late Thrombosis – Myocardial infarction occurring >30 days after the index procedure and attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and freedom from an interim revascularization of the target vessel.

Subacute (Subabrupt) Closure – Abrupt closure that occurred after the index procedure was completed (and the patient left the catheterization laboratory) and before the 30-day follow-up endpoint.

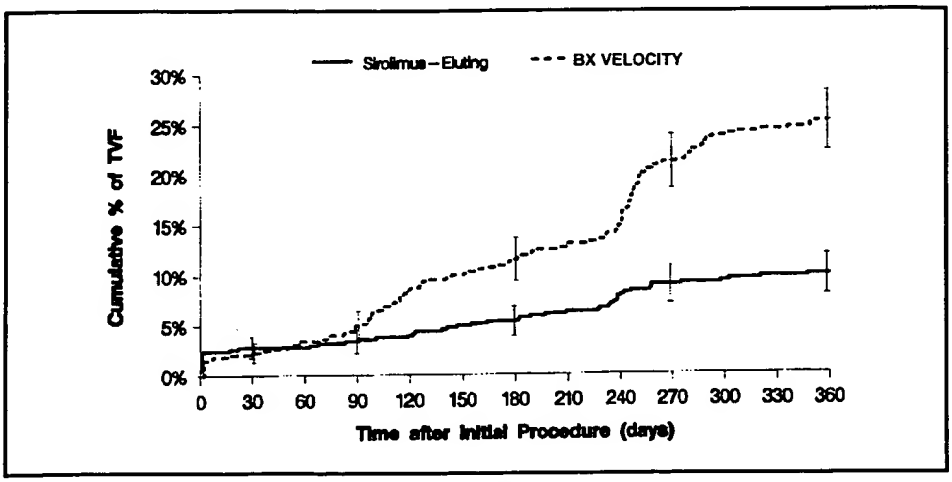
Cerebrovascular Accident (CVA) – Sudden onset of vertigo, numbness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours.

Major Bleeding Complications – Bleeding requiring transfusions or associated with hemoglobin drop > 5.0 g/dL.

Major (hemorrhagic) Vascular Complication – Hematoma at access site >5 cm; false aneurysm; AV fistula; retroperitoneal bleed; peripheral ischemia/nerve injury; any transfusion required was reported as a vascular complication unless clinical indication clearly other than catheterization complication; and vascular surgical repair.

[2] SAS is a trademark of SAS Institute, Inc.

Figure 8-1
Kaplan-Meier Graph and Life Table to 360 Days
SIRIUS Cumulative Percentage of Target Vessel Failure



Error Bars indicate 1.5 Standard Error

	Time after initial procedure (days)												
	0	7	14	30	60	90	120	150	180	210	240	270	360
Sirolimus-Eluting Bx VELOCITY™													
# Entered	533	530	519	519	517	514	509	505	499	496	490	481	474
# Censored	0	1	0	0	3	2	1	1	1	1	1	1	20
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# at risk	533.0	529.5	519.0	519.0	515.5	513.0	508.5	504.5	498.5	495.5	489.5	480.5	464.0
# Events	3	10	0	2	0	3	3	5	2	5	8	6	5
# Events/Month		42.9	0.0	3.8	0.0	3.0	3.0	5.0	2.0	5.0	8.0	6.0	1.7
% with Events	0.6%	2.4%	2.4%	2.8%	2.8%	3.4%	4.0%	4.9%	5.3%	6.2%	7.8%	8.9%	9.9%
SE	0.3%	0.7%	0.7%	0.7%	0.7%	0.8%	0.9%	0.9%	1.0%	1.1%	1.2%	1.2%	1.3%
Bx VELOCITY™													
# Entered	525	525	515	515	513	507	499	475	468	460	450	439	406
# Censored	0	0	0	0	0	0	4	0	1	2	0	2	19
# Incomplete	0	0	0	0	0	0	0	0	0	0	0	0	0
# at risk	525.0	525.0	515.0	515.0	513.0	507.0	497.0	475.0	467.5	459.0	450.0	438.0	396.5
# Events	0	10	0	2	6	8	20	7	7	8	11	31	20
# Events/Month		42.9	0.0	3.8	6.0	8.0	20.0	7.0	7.0	8.0	11.0	31.0	6.7
% with Events	0.0%	1.9%	1.9%	2.3%	3.4%	5.0%	6.8%	10.1%	11.5%	13.0%	15.1%	21.1%	25.1%
SE	0.0%	0.6%	0.6%	0.7%	0.8%	1.0%	1.3%	1.4%	1.4%	1.5%	1.6%	1.8%	2.0%

Tests Between Groups

Test	Chi-Square	Deg Frdm	P-value
Log-Rank	40.01	1	<0.001
Wilcoxon	38.29	1	<0.001

Standard error estimates by Peto formula.

8.3. RAVEL Trial

Purpose: The purpose of the trial was to evaluate the safety and effectiveness of the **CYPHER** Stent for reducing late loss in *de novo* native coronary artery lesions.

Conclusions: In selected patients, use of the **CYPHER** Stent significantly reduced the rate of in-stent late loss at 6 months compared to the Control (**BX VELOCITY**, an uncoated 316L stainless steel stent). Clinical outcomes at 24 months were also significantly improved.

Design: This was a multi-center, prospective, randomized, double-blind trial conducted at 19 sites in Europe, Brazil and Mexico. The primary efficacy endpoint was pre-specified to be in-stent late loss at 6 months. To be eligible a patient was required to have a *de novo* ischemic lesion of a length that could be covered by a single 18 mm stent in a native coronary artery of diameter 2.5 mm to 3.5 mm (using visual estimates).

Patients were randomized with equal probability to receive either the **CYPHER** Stent or the Control stent. A total of 238 patients were randomized; 120 to **CYPHER** Stent and 118 to Control. After the procedure patients were treated with aspirin indefinitely and with clopidogrel or ticlopidine for 2 months.

Angiographic follow-up at 6 months was obtained on 217 patients. IVUS follow-up (but without baseline studies) was obtained on 110 patients. Clinical follow-up is currently available through 2 years (± 1 month) in 90% of patients.

Demography: Baseline characteristics were similar for both treatment arms; factors evaluated included age (mean 61 years), diabetes (18%), prior MI (36%), hypertension (49%), hyperlipidemia (52%), current smoking (30%), CSS Angina Class (12% III or IV), IIb/IIIa inhibitor use (10%), LAD (50%), LCX (23%), RCA (27%), reference vessel diameter (mean 2.6 mm), minimum lumen diameter (mean 0.95 mm), percent diameter stenosis (mean 64%), and lesion length (mean 9.6 mm). Overall 24% were female, but there were more women in the **CYPHER** Stent arm (30%) than in the Control arm (19%); gender was not a significant predictor of outcome in the trial.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms by clinical coordinators at the clinical sites. Angiographic and IVUS outcomes were assessed in a blinded fashion by quantitative analysis at designated central laboratories. An independent review committee adjudicated clinical events, and the trial was monitored by an independent Data and Safety Monitoring Committee.

Results: In selected patients, elective **CYPHER** Stent placement in native coronary *de novo* lesions resulted in significantly lower in-stent late loss at 6 months compared to control (-0.01 mm vs. 0.80 mm, $p < 0.001$), and the mean in-lesion % diameter stenosis also was significantly reduced (25.3% vs. 38.7%, $p < 0.001$). There was no evidence of an edge-effect 5 mm proximal or distal to the stent. Examination by IVUS at 6 months showed that neointima volume was significantly reduced in the **CYPHER** Stent arm (1.5 mm^3 vs. 34.3 mm^3, $p < 0.001$), but there was a higher rate of incomplete stent apposition (21% vs. 4%, $p = 0.028$). The rate of target vessel failure by 1 year was lower (4% vs. 20%, $p < .001$).

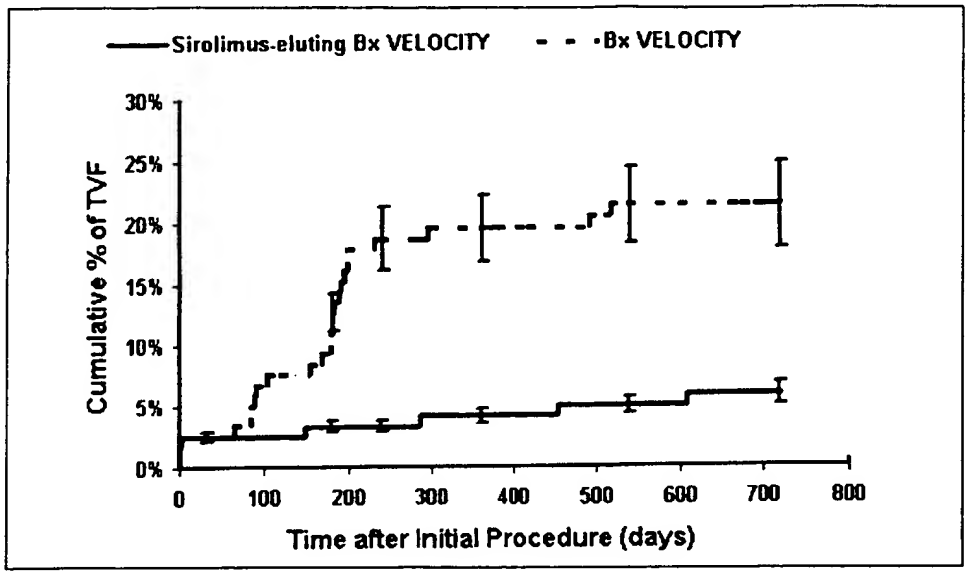
Table 8-3 summarizes the principal effectiveness and safety results of the RAVEL Trial to 720 days. Figure 8-2 provides the cumulative TVF rates to 720 days.

Table 8-3: RAVEL Principal Effectiveness and Safety Results (to 720 days)
All Patients Treated (N=238)

Effectiveness Measures	CYPHER Stent (N=120)	Control (N=118)	Difference [95% CI]	P-value
Procedure Success	96.7% (116/120)	93.1% (108/116)	3.6% [-2.1%, 9.2%]	0.248
Binary Restenosis Rate	0.0% (0/109)	26.6% (29/109)	-26.6% [-34.9%, -18.3%]	<0.001
Post-procedure MLD (mm)				
In-stent	2.43 ± 0.41 (N=120)	2.41 ± 0.40 (N=116)	0.01 [-0.09, 0.12]	0.705
In-lesion	1.97 ± 0.40 (N=120)	2.01 ± 0.44 (N=116)	-0.04 [-0.14, 0.07]	0.465
Post-procedure % DS				
In-stent	11.9 ± 5.9 (N=120)	14.0 ± 6.8 (N=116)	-2.1 [-3.7, -0.5]	0.012
In-lesion	24.5 ± 8.6 (N=120)	24.7 ± 10.7 (N=116)	-0.2 [-2.7, 2.2]	0.855
6 month f/u MLD (mm)				
In-stent	2.42 ± 0.49 (N=109)	1.64 ± 0.59 (N=109)	0.78 [0.64, 0.93]	<0.001
In-lesion	2.01 ± 0.47 (N=109)	1.57 ± 0.53 (N=109)	0.45 [0.31, 0.58]	<0.001
6 month f/u % DS				
In-stent	14.7 ± 6.9 (N=109)	36.7 ± 18.0 (N=109)	-22.0 [-25.6, -18.4]	<0.001
In-lesion	25.3 ± 9.6 (N=109)	38.7 ± 16.9 (N=109)	-13.5 [-17.1, -9.8]	<0.001
6 month f/u				
Late loss (mm)	-0.01 ± 0.33 (N=109)	0.80 ± 0.53 (N=108)	-0.81 [-0.93, -0.70]	<0.001
Volume obstruction in-stent (mm)	1.1 ± 2.5 (N=56)	26.1 ± 20.2 (N=54)	-25.0 [-30.3, -19.7]	<0.001
TLR-Free to 720 days*	97.4%	86.2%	11.2% [3.7%, 18.7%]	0.001
TVR-Free to 720 days*	96.6%	83.6%	13.0% [4.9%, 21.1%]	<0.001
TVF-Free to 720 days*	94.1%	78.7%	15.4% [6.2%, 24.6%]	<0.001
MACE-Free to 720 days*	89.9%	80.4%	9.5% [0.0%, 19.2%]	0.022
Safety Measures				
MACE in-Hospital	2.5% (3/120)	2.5% (3/118)	0.0% [-4.0%, 3.9%]	1.000
MACE out-of-Hospital to 720 days	7.5% (9/120)	17.8% (21/118)	-10.3% [-18.7%, -1.9%]	0.019
MACE to 720 days	10.0% (12/120)	19.5% (23/118)	-9.5% [-18.4%, -0.6%]	0.045
Sub-acute Occlusion	0.0% (0/120)	0.0% (0/118)	0.0% [—,—]	--
Stent Thrombosis	0.0% (0/120)	0.0% (0/118)	0.0% [—,—]	--
Late Thrombosis	0.0% (0/120)	0.0% (0/118)	0.0% [—,—]	--
CVA to 720 days	0.8% (1/120)	0.0% (0/118)	0.8% [-0.8%, 2.5%]	1.000
Major Bleeding Complications to 720 days	0.8% (1/120)	3.4% (4/118)	-2.6% [-6.2%, 1.1%]	0.211

Numbers are % (counts/available field sample size) or mean ± 1 standard deviation.
CI = Confidence Interval — CI = Diff ± 1.96 • SE
SD = Standard Deviation — SE = sqrt (p1•q1/n1 + p2•q2/n2)
Procedure success – Successful implantation of study device, attainment of < 30% diameter stenosis by angiographic corelab. Quantitative Coronary Angiography (QCA) determination, and freedom from in-hospital MACE.
% DS— Percent diameter stenosis – value calculated as 100•(1-MLD/RVD) using the mean values from two orthogonal views (when possible) by Quantitative Coronary Angiography (QCA). A 100% DS was imputed for total occlusions if no RVD values were available.
Restenosis Rate – Percent lesions with a follow-up percent diameter stenosis is ≥ 50%.
* The following survival estimates are by Kaplan-Meier methods. Standard Error estimates from Peto formula.
TLR–Free – No target lesion revascularization
TVR-Free – No target vessel revascularization
TVF-Free – No cardiac death, target vessel related myocardial infarction or target vessel revascularization
MACE-Free – No death, myocardial infarction, target lesion CABG or target lesion Re-PTCA
In-Hospital MACE – Death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization prior to hospital discharge as determined by the independent Clinical Events Committee.
Out-of-Hospital MACE - Death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization after hospital discharge through the 720 days contact as determined by the independent Clinical Events Committee.
Late loss— Difference MLD after device— MLD at follow-up.
MACE – Major Adverse Cardiac Events: death, myocardial infarction (Q-wave and non Q-wave), target lesion CABG or target lesion revascularization.
Major Bleeding Events – Any intracranial bleeding, cardiac tamponade, bleeding events associated with a decrease in hemoglobin > 5.0 g/dL, transfusion or surgical repair.
MI – Myocardial Infarction: Necrosis of the myocardium, as a result of interruption of the blood supply to the area as in coronary thrombosis. For this study, myocardial infarction was categorized in Q-wave and non Q-wave.
Sub-acute occlusion – New reduced (TIMI 0 or 1) flow at the target vessel as a result of mechanical obstruction, such as dissection or luminal thrombus, occurring after completion of the index procedure but within thirty days of stent deployment.
Stent Thrombosis – Complete thirty-day ischemic endpoint including death, Q-wave MI or subabrupt closure requiring revascularization.
Late Thrombosis – Late Thrombosis was myocardial infarction attributable to the target vessel with angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site > 30 days after the index procedure in the absence of an intervening revascularization of the target vessel.
MLD – mean minimal luminal diameter (mm) from two orthogonal views using Quantitative Coronary Angiography (QCA).
RVD – Reference Vessel Diameter: Average of normal segments proximal and distal to the target lesion from two orthogonal views (when available) using QCA.
TL = Target Lesion
TV = Target Vessel
CVA = Cerebrovascular Accident: Cerebral hemorrhage, thrombosis, or embolism leading to neurological deficit.

Figure 8-2
Kaplan-Meier Graph and Life Table to 720 Days
RAVEL Cumulative Percentage of Target Vessel Failure



Error Bars Indicate ± 1.5 Standard Error
Standard Error based on the Peto formula

Target Vessel Failure Life Table Analysis: All Patients Treated (N=238)

Interval ending day	0	2	7	30	60	120	180	240	300	360	420	480	540	600	660	720
Sirolimus-eluting Bx VELOCITY™ (N=120)																
# Entered	120	120	117	117	117	117	117	116	116	115	113	111	110	108	106	101
# Censored	0	0	0	0	0	0	0	0	0	2	2	0	2	2	4	21
# At risk	120	120	117	117	117	117	117	116	116	114	112	111	109	107	104	91
# Events	0	3	0	0	0	0	1	0	1	0	0	1	0	0	1	0
# Events / Month	0	45.0	0.0	0.0	0.0	0.0	0.5	0.0	0.5	0.0	0.0	0.5	0.0	0.0	0.5	0.0
% with Events	0.0	2.5	2.5	2.5	2.5	2.5	3.3	3.3	4.2	4.2	4.2	5.0	5.0	5.0	5.9	5.9
Std. Err. (%)	0.0	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6
Bx VELOCITY™ (N=118)																
# Entered	118	118	115	115	115	115	109	105	96	93	92	88	88	85	85	85
# Censored	0	0	0	0	0	0	0	0	2	1	4	0	1	0	0	17
# At risk	118	118	115	115	115	115	109	105	95	93	90	88	88	85	85	77
# Events	0	3	0	0	0	6	4	9	1	0	0	0	2	0	0	0
# Events / Month	0	45.0	0.0	0.0	0.0	3.0	2.0	4.5	0.5	0.0	0.0	0.0	1.0	0.0	0.0	0.0
% with Events	0.0	2.5	2.5	2.5	2.5	7.6	11.0	18.6	19.5	19.5	19.5	19.5	21.3	21.3	21.3	21.3
Std. Err. (%)	0.0	0.2	0.2	0.2	0.2	0.7	1.0	1.7	1.8	1.8	1.9	1.9	2.1	2.1	2.1	2.3

Survival Curves Comparison

	Log-Rank P-value	Wilcoxon P-Value
Life-Table Analysis	<0. 001	<0. 001
Kaplan-Meier Analysis	<0. 001	<0. 001

Standard error estimates from Peto formula

8.4. First-in-Man Study

Purpose: The purpose of this early feasibility study was to evaluate the performance of the **CYPHER** Stent and an alternate formulation sirolimus-eluting stent in *de novo* native coronary artery lesions. This study provides the longest follow-up experience available.

Conclusions: In selected patients, use of the **CYPHER** Stent provided favorable IVUS, angiographic and clinical results through 24 months of follow-up.

Design: This was a non-randomized, open-label study conducted at two sites, one in The Netherlands and one in Brazil. To be eligible, a patient was required to have a *de novo* ischemic lesion of a length that could be covered by a single 18 mm stent in a native coronary artery of diameter 3.0 mm to 3.5 mm (using visual estimates). A total of 45 patients were treated, of which 30 received the **CYPHER** Stent and 15 received an alternative formulation sirolimus-eluting stent. After the procedure, patients were treated with aspirin indefinitely and with clopidogrel for 2 months. Angiographic follow-up was performed at 4, 12 and 24 months, or at 6 and 18 months, depending on the site. Angiographic follow-up is available for 24 patients, and IVUS follow-up is available for 15 patients. Clinical follow-up is available through 2 years.

Demography: Patients had a mean age of 58 years, there were 36% females, and 13% had diabetes, 51% of the lesions treated were in LAD, 22% were in the LCX, 27% were in the RCA, mean reference vessel diameter was 2.9 mm, mean minimum lumen diameter was 0.95 mm, mean percent diameter stenosis was 67%, and 27% of patients had a lesion length < 10 mm and 73% of patients had a lesion length between 10 and 18 mm. **Note:** IIb/IIIa inhibitor usage was not monitored during this study.

Methods: Baseline clinical and angiographic data were collected on standardized case report forms. Angiographic and IVUS outcomes were assessed by quantitative analysis at designated central laboratories. An independent Clinical Events Committee adjudicated clinical events.

Results: At 18 to 24 months following elective **CYPHER** Stent placement in native coronary *de novo* lesions, in-stent mean % diameter stenosis ranged from 1.4% to 3.2%, and mean in-stent late loss ranged from -0.09 mm to 0.20 mm. Mean obstructive volume by IVUS ranged from 2.3% to 7.5%. The overall MACE rate at 24 months was 10%.

Table 8-4: First-in-Man: Effectiveness and Safety Results
All Patients Treated with CYPHER Stent

Effectiveness Measures	CYPHER Stent (N=30 Patients, N=30 Lesions)
Procedure Success (QCA)	100.0% (30/30)
% Diameter Stenosis	
18 Months (The Netherlands)	3.2% ± 13.1% (10)
24 Months (Brazil)	1.4% ± 5.9% (14)
In-Stent Late Loss (mm)	
18 Months (The Netherlands)	0.20 ± 0.24 (10)
24 Months (Brazil)	-0.09 ± 0.24 (14)
Obstruction Volume (%)	
18 Months (The Netherlands)	2.3% ± 2.1% (7)
24 Months (Brazil)	7.5% ± 7.3% (8)
24-month Target Lesion Revascularization (TLR)	3.3% (1/30)
Safety Measures	
In-Hospital MACE Events	6.7% (2/30)
Out-of-Hospital MACE Events to 24 months	3.3% (1/30)
Combined (In and Out-of-Hospital) MACE to 24 months	10.0% (3/30)

Numbers are % (counts available field sample size) or Mean ± Standard Deviation.
Procedure Success – The attainment of a final in-stent diameter stenosis of <50% (by QCA) in the absence of death, emergent CABG, Myocardial Infarction, or TLR prior to hospital discharge.
QCA – Quantitative Coronary Angiography by Corelab
MACE is a composite endpoint comprised of deaths, WHO-defined non Q-wave myocardial infarction, Q-wave myocardial infarction, or target lesion revascularization.

9. Individualization of Treatment
See also **Precautions– 5.5 Use in Special Populations** and **Precautions– 5.6 Lesion/Vessel Characteristics**.

The risks and benefits described above should be considered carefully for each patient before use of the **CYPHER** Stent. Patient selection factors to be assessed should include a judgment regarding the risk of prolonged anticoagulation. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease, see Section 3 – **Contraindications**).

Premorbid conditions that increase the risk of a poor initial result and the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed. The relation of baseline and procedural variables to Major Adverse Cardiac Events (MACE) was examined. Multivariable modeling suggested that treatment assignment remained an independent predictor of clinical and angiographic outcomes even after adjusting for other baseline and procedural confounding variables.

10. Patient Counseling Information
Physicians should consider the following in counseling patient about this product:
- Discuss the risks associated with stent placement
- Discuss the risks associated with a sirolimus-eluting implant
- Discuss the risks/benefits issues for this particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long term.

11. How Supplied
STERILE: This device is sterilized with ethylene oxide gas and is nonpyrogenic. Do not use if the package is opened or damaged. For one use only. Do not resterilize.

CONTENTS: One (1) **CYPHER** Sirolimus-eluting Coronary Stent on **RAPTOR** Over-the-Wire Delivery System or **RAPTORRAIL** Rapid Exchange Delivery System.

STORAGE: Store in a cool, dark, dry place. Store at 25°C (77°F); excursions permitted to 15-30°C (59 – 86°F).

12. Operator's Manual (Combined OTW and RX)

12.1. Access to Package Holding Sterile Stent Delivery System

Tear open the foil pouch to remove the product that is packaged in a coiled hoop and tray. Pass or drop the product into the sterile field using an aseptic technique.

12.2. Inspection Prior to Use

Before opening, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Prior to using the device, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the device if any damage to the packaging is noted.

12.3. Materials Required

Quantity	Material
N/A	Appropriate guiding catheter(s)
2-3	10-20 cc syringes
1,000 u /500 cc	Sterile Heparinized Normal Saline (HepNS)
1	0.014" (0.36 mm) diameter guidewire (**OTW**: 300 cm long)
1	Rotating hemostatic valve with an appropriate internal diameter (OTW: min. I.D. of 0.074" [1.9 mm]) (RX: min. I.D. of 0.096" [2.4 mm])
N/A	Contrast diluted 1:1 with normal saline
1	Inflation device
1	Stopcock (3-way minimum)
1	Torque device
1	Guidewire Introducer
N/A	Appropriate anticoagulation and anti-platelet drugs

12.4. Preparation

Precaution

- AVOID manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.
- DO NOT apply negative or positive pressure to the balloon during the delivery system preparation.

12.4.1. Rinse the catheter with sterile heparinized normal saline solution.

12.4.2. Guidewire Lumen Flush

OTW	1. Locate the guidewire lumen hub and flush the guidewire lumen with HepNS.
RX	1. Attach the syringe with HepNS to the flushing needle packaged with the catheter. 2. Insert the needle into the tip of the catheter and flush the guidewire lumen with HepNS.

12.4.3. Delivery System Preparation

Step	Action
1.	Prepare the inflation device or syringe with diluted contrast medium.
2.	Attach the inflation device or syringe to the stopcock; attach to the balloon inflation port hub.
3.	Open the stopcock to **stent delivery system.**
4.	Leave the inflation device or syringe on neutral.

12.5. Delivery Procedure

Step	Action
1.	Prepare the vascular access site according to standard practice.
2.	**Predilate the lesion with a PTCA catheter.** Limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the **CYPHER** Stent.
3.	Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible.
4.	Backload the delivery system onto the proximal portion of the guidewire while maintaining the guidewire position across the target lesion.
5.	Advance the stent delivery system over the guidewire to the target lesion. Use the radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm the position of the stent.

Note: Should **unusual resistance** be felt **at any time** during either lesion access or removal of the stent delivery system before stent implantation, the entire system should be **removed as a single unit.** See **Precautions – 5.14 Stent/System Removal Precautions** for specific stent delivery system removal instructions.

12.6. Deployment Procedure

Step	Action
1.	Before deployment, reconfirm the correct position of the stent relative to the target lesion via the radiopaque balloon markers.
2.	Attach the inflation device (only partially filled with contrast media) to a three-way stopcock and apply negative pressure to purge the balloon of air.
3.	Turn the stopcock on the catheter to the off position and purge the inflation device of air. Close the side port of the stopcock.
4.	Under fluoroscopic visualization, inflate the balloon to at least the nominal pressure to deploy the stent, but **do not exceed the labeled rated burst pressure of 16 atm (1621 kPa).** Optimal expansion requires the stent to be in full contact with the artery wall, with the stent internal diameter matching the size of the reference vessel diameter. Stent wall contact should be verified through routine angiography or intravascular ultrasound.
5.	Fully cover the entire lesion and balloon treated area (including dissections) with the **CYPHER** Stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion.
6.	If more than one **CYPHER** Stent is needed to cover the lesion and balloon treated area, adequately overlap stents, taking into account stent foreshortening. Ensure no gaps between stents by positioning the balloon marker bands of the second **CYPHER** Stent inside the deployed stent prior to expansion. See **Precautions – 5.14 Stent/System Removal Precautions.**
7.	Deflate the balloon by pulling a vacuum with the inflation device. Make certain that the balloon is fully deflated before attempting to move the catheter.
8.	Confirm that the stent is adequately expanded by angiographic injection through the guiding catheter.

12.7. **Further Dilatation of Stented Segments**
Precaution: Do not dilate the stent beyond the following limits:

Nominal Stent Diameter	Dilatation Limits
2.50 mm – 3.00 mm	3.75 mm
3.50 mm	4.75 mm

All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

12.8. **Removal Procedure**

Step	Action
1.	Ensure that the balloon is fully deflated.
2.	While maintaining the guidewire position and negative pressure on the inflation device, withdraw the stent delivery system. **Note:** Should **unusual resistance** be felt at **any time** during either lesion access or removal of stent delivery system before stent implantation, the entire system **should be removed as a single unit.** See **Precautions – 5.14 Stent/System Removal Precautions** for specific stent delivery system removal instructions.
3.	Repeat angiography to assess the stented area. If an adequate expansion has not been obtained, exchange back to the original stent delivery catheter or exchange to another balloon catheter of appropriate balloon diameter to achieve proper stent apposition to the vessel wall.
4.	The final stent diameter should match the reference vessel. ASSURE THAT THE STENT IS NOT UNDERDILATED.

12.9. ***In-vitro* Information**

Table 12-1 Inflation Pressure Recommendations

Inflation Pressure atm (kPa)	2.50	2.75	3.00	3.50	
6 (608)	2.20	2.44	2.71	3.20	
7 (709)	2.27	2.51	2.78	3.27	
8 (811)	2.33	2.58	2.84	3.33	
9 (912)	2.39	2.64	2.90	3.39	
10 (1013)	2.45	2.70	2.95	3.45	
11 (1115)	2.50	2.75	3.00	3.50	Nominal
12 (1216)	2.55	2.80	3.05	3.55	
13 (1317)	2.59	2.84	3.09	3.60	
14 (1419)	2.62	2.88	3.13	3.64	
15 (1520)	2.66	2.92	3.16	3.69	
16 (1621)	2.69	2.95	3.19	3.73	RBP
17 (1723)	**2.71**	**2.98**	**3.22**	**3.76**	
18 (1824)	**2.73**	**3.00**	**3.24**	**3.79**	
19 (1925)	**2.74**	**3.02**	**3.25**	**3.82**	
20 (2026)	**2.75**	**3.03**	**3.27**	**3.85**	

Note: These nominal, *in vitro*, device specifications do not take into account lesion resistance. The stent sizing should be confirmed angiographically. Do not exceed the rated burst pressure (RBP). These data are based on *in vitro* testing at 37°C. Bolded text represents diameters at pressures above the rated burst pressure. These values are within ± 10% of the labeled diameter between the nominal pressure and the rated burst pressure.

13. **Patient Information**
In addition to this Instructions for Use booklet, the following patient specific information regarding the **CYPHER** Sirolimus-eluting Coronary Stent is available:
- A Patient Implant Card that includes both patient and **CYPHER** Sirolimus-eluting Coronary Stent specific information. All patients will be expected to keep this card in their possession at all times for procedure / stent identification.
- A Patient Information Guide, which includes information on the implant procedure, and the **CYPHER** Sirolimus-eluting Coronary Stent System.

14. **Patents**
Protected under one or more of the following U.S. patent Nos.: 4,597,755; 4,733,665; 4,739,762; 4,748,982; 4,775,371; B1 4,776,337; 4,782,834; 4,906,244; 4,927,418; 4,938,220; 4,981,478; 5,017,325; 5,040,548; 5,061,273; 5,102,417; 5,108,415; 5,135,535; 5,154,725; 5,156,612; 5,176,661; 5,223,205; 5,234,416; 5,236,659; 5,242,396; 5,288,711; 5,290,230; 5,300,025; 5,300,085; 5,304,197; 5,316,706; 5,346,505; 5,350,395; 5,356,591; 5,387,193; 5,413,559; 5,433,713; 5,439,447; 5,449,371; 5,451,209; 5,451,233; 5,458,613; 5,480,383; 5,496,275; 5,496,346; 5,498,240; 5,501,227; 5,516,781; 5,538,510; 5,554,121; 5,563,146; 5,585,057; 5,626,600; 5,643,279; 5,643,312; 5,646,160; 5,665,728; 5,685,312; 5,697,971; 5,709,658; 5,738,653; 5,743,875; 5,749,888; 5,769,868; 5,807,355; 5,868,706; 5,879,370; 5,902,332; 6,010,521; 6,013,069; 6,027,475; 6,036,715; 6,086,604; 6,110,142 and other patents pending in the U.S. and other countries.

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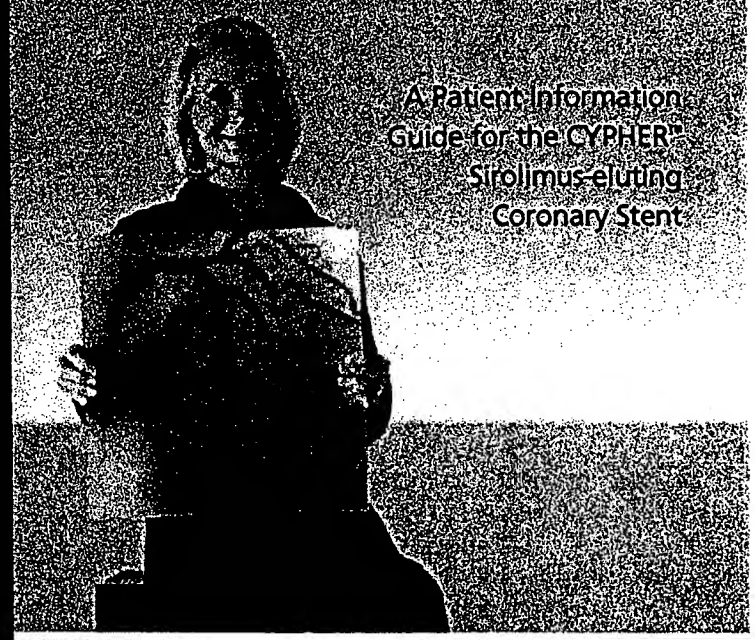
 April 2005 155-0736-1

Understanding Coronary Artery Disease, Cardiac Catheterization, and Treatment Options

A Patient Information Guide for the CYPHER™ Sirolimus-eluting Coronary Stent



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Introduction

You have an important role to play in order to ensure that your procedure will be successful. Thoroughly read this booklet, cooperate with your physician and follow through with your responsibilities as part of the patient/medical team.

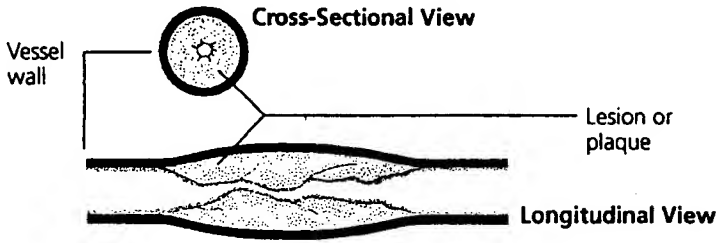
Table of Contents

Coronary Artery Disease

If you or a member of your family has been diagnosed with coronary artery disease (CAD), you may have questions about the disease and its treatment, especially if your doctor has recommended angioplasty followed by implantation of a drug-eluting coronary stent. This booklet answers some of the questions patients with coronary artery disease often ask.

- **Angioplasty** - A balloon procedure to open an obstruction or narrowing of a blood vessel. Also known as percutaneous transluminal coronary angioplasty (PTCA).

- **Stent** - An expandable, slotted metal tube, inserted into a vessel. A stent acts as a scaffold to provide structural support for a vessel. A drug-*eluting* stent allows for the active release of that particular drug at the stent implantation site.



Plaque partially blocking artery

Atherosclerosis A disease process in which fatty substances (plaque), such as cholesterol, are deposited on the inner lining of blood vessels.

Angina (Pectoris) Chest discomfort, pain, tightness or pressure. May also have associated pain in neck, jaw, back or arm. May include profuse sweating, nausea, or shortness of breath. Angina may be a single symptom or a combination of these symptoms.

What Causes Coronary Artery Disease?

The heart is a muscle that acts like a pump to move blood throughout the body. To function properly, the heart must receive oxygen. Oxygen is supplied to the heart by the coronary (heart) arteries that wrap around the surface of the heart. When coronary artery disease (CAD) is present, blood flow through the arteries can be reduced. When this happens, the heart muscle may not receive enough oxygen, and chest pain (called angina) may be felt.

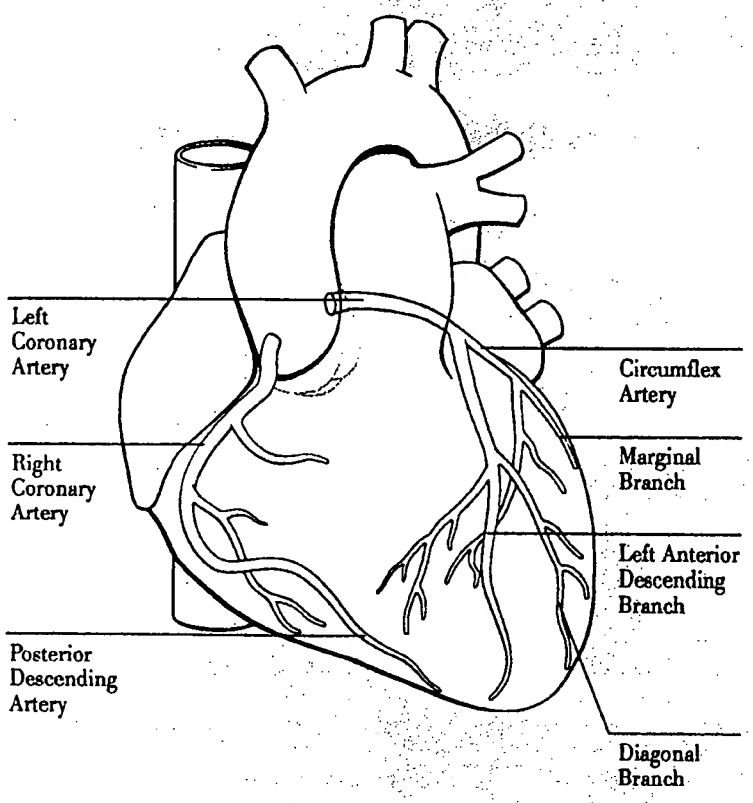
CAD is caused by the build-up of fatty substances, such as cholesterol, that collect along the lining of the coronary arteries, in a process known as atherosclerosis. You may hear this referred to as a "plaque", "lesion", "blockage" or "stenosis". This means that there is a narrowing in the artery caused by a build-up of substances which may eventually block the flow of blood. Because the coronary arteries supply oxygen-rich blood to the heart, untreated blockages can be very serious and can lead to a heart attack (myocardial infarction) or even death. Over the course of a person's lifetime many influences can cause one or more of your coronary arteries to become narrowed or blocked.

Coronary Arteries The coronary arteries are special blood vessels which supply the heart with necessary oxygen and nutrients. The heart does not function properly without enough oxygen.

Coronary Artery Disease Atherosclerosis of the coronary arteries.

Myocardial Infarction Commonly called a "heart attack". Involves irreversible damage to heart tissue/muscle. Insufficient oxygen reaching the heart muscle via the coronary arteries may cause angina, heart attack (myocardial infarction), or even death to the affected area of the heart.

The Heart and Its Coronary Arteries



Symptoms of Heart Disease

Coronary artery disease can progress very slowly, often without symptoms. Most people do not realize that they have heart disease. In fact, the first sign that something may be wrong could be an episode of angina, or even a heart attack. Typical angina symptoms are feelings of pressure, tightness, or pain in the chest, arm, back, neck or jaw. Symptoms also include heartburn, nausea, vomiting, excessive sweating, fatigue or shortness of breath. Angina may occur as only one or many of these symptoms.

Although the exact cause of CAD is not known, there are certain risk factors that are often seen in patients with coronary artery disease. These factors include: high blood pressure, having a close relative with heart disease, high cholesterol and/or triglycerides in your blood, diabetes, smoking, excessive weight, and lack of a regular exercise program. Males are more likely to develop coronary artery disease than females.

Risk Factors for CAD

You are at greatest risk for CAD if you:

- are male
- have high blood pressure
- are diabetic
- smoke cigarettes
- are overweight and/or inactive
- have a relative with the disease

Cholesterol A substance that circulates in the blood and plays a role in the formation of blockages. Cholesterol originates in foods that are rich in animal fats.

Diabetes A disease affecting one's metabolism of glucose (sugar) which causes changes in blood vessels. These changes may aid in the development of coronary artery disease.

Triglycerides Substances in the blood that are a component of the "bad" type of cholesterol.

How is Heart Disease Diagnosed?

You may have experienced symptoms of heart disease which caused you to seek your doctor's attention. If you have experienced symptoms or have an increased risk of heart disease, your doctor may recommend that you have an exercise stress test, an electrocardiogram (EKG), chest x-ray, and blood tests. Stress tests measure changes in the electrical activity of your heart as you perform controlled exercise, and may show if heart muscle is at risk of dying or if there has been damage to your heart. These results may indicate a need for further testing. Your doctor may then recommend a cardiac catheterization or coronary angiogram. It is one of the most useful methods to diagnose coronary artery disease because it allows the doctor, under x-ray, to see exactly where the coronary arteries are narrowed or blocked.

- **Cardiac** - Relating to the heart.
- **Catheterization** - A procedure that involves passing a tube (catheter) through blood vessels and injecting dye to detect blockages.
- **Coronary Angiogram** - A test used to diagnose CAD using the catheterization procedure. Contrast dye is injected into the coronary arteries via a catheter, and this allows the doctor to see, on an x-ray screen, the exact site where the artery is narrowed or blocked.

Catheter A tube used for gaining access to one of the body's cavities or blood vessels. In angioplasty, a catheter provides access to the heart's arteries.

Electrocardiogram (EKG) A test that measures and shows the electrical activity of the heart muscle.

Stress Test A test that measures electrical changes in the patient's heart (EKG) while the patient is doing controlled exercise. The stress test can show if there has been damage to the heart or if there is decreased blood flow to areas of the heart.

Cardiac Catheterization

Cardiac catheterization is performed in a specialized area in the hospital called a Cardiac Catheterization Laboratory. The night prior to the test, you may not be allowed to eat or drink anything after midnight. Before the catheterization, a doctor will explain the procedure to you and ask certain questions about your health. While you are discussing this test, you should ask any questions or mention any concerns or worries that you have about the procedure. After the procedure has been explained, you will be asked to sign a consent form, which gives your permission for the test to be performed.

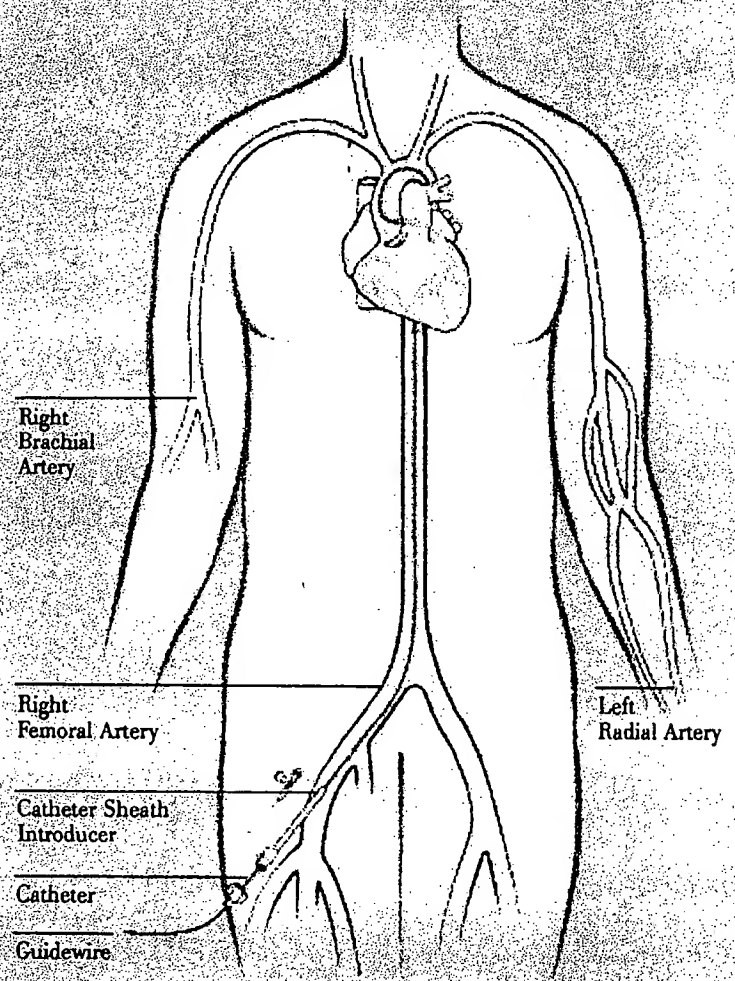
Before your procedure begins, you will be taken to the room where the cardiac catheterization will be done. Your heart rhythm will be monitored and an intravenous line (IV) will be placed to provide you with fluids and to make it easier to administer any needed medication.

Your arm or groin will be shaved and cleaned with an antiseptic solution and sterile drapes will be placed in this area. Before the procedure begins, you will receive local anesthetic to numb the area. You may feel some pressure and a burning sensation at the site, but it will only last a few seconds.

During the procedure you will not need general anesthesia, but a sedative may be given to help you relax. It is important for you to remain awake so that you can move or breathe deeply when asked to do so by the doctor. Following these instructions may improve the quality of the x-ray pictures.

During this procedure a long tube called a catheter is placed through another small tube, (called a catheter sheath introducer) that is inserted in your arm or groin. The catheter is guided to your heart and then into the opening of the arteries. The catheter provides a pathway for a special liquid dye to flow into the arteries. This liquid dye allows the doctor to see the shape

In coronary angiography, a catheter is inserted into an artery and then guided to your heart.



and size of your arteries as well as the function of your heart muscle on an x-ray screen.

Once the catheter is positioned, the doctor will take pictures of your heart. With the catheter in the main pumping chamber of the heart (left ventricle), some dye will be injected through the catheter and a picture will be taken. The dye makes it easier for the doctor to see the shape and overall function of your heart. You may be asked to take a deep breath and hold it, which allows the doctor to have a clearer view of your heart on the x-ray screen. You may also feel a hot flush when the dye is injected. This feeling is to be expected and normally passes in 15 to 30 seconds.

Pictures will also be taken of your coronary arteries from several different angles. Once all these pictures have been developed and your doctor has been able to review them, he or she will be able to discuss the final results with you. If the cardiac catheterization showed that there were one or more blockages in your coronary arteries, then further treatment may be recommended.

Can Heart Disease Be Treated?

Most patients with heart disease receive medication to help prevent a heart attack, and doctors usually recommend controlled exercise and a low-fat diet. Medication may also be prescribed to help lower cholesterol levels in the blood. However, there are no drugs available to eliminate blockages within the heart arteries. If heart disease is present, you may be at risk of having a heart attack if the disease is not treated. Until several years ago, the only treatment for blockages of heart arteries was Coronary Artery Bypass Graft (CABG) surgery.

Today, there are several options available to you. Your doctor can discuss these with you to determine which option is best for you.

Balloon Angioplasty

This procedure may be done immediately following your catheterization or you may be sent home and instructed to return for the procedure. You will be asked not to eat or drink anything after midnight on the night before your procedure. It is important that you follow these and any other instructions carefully.

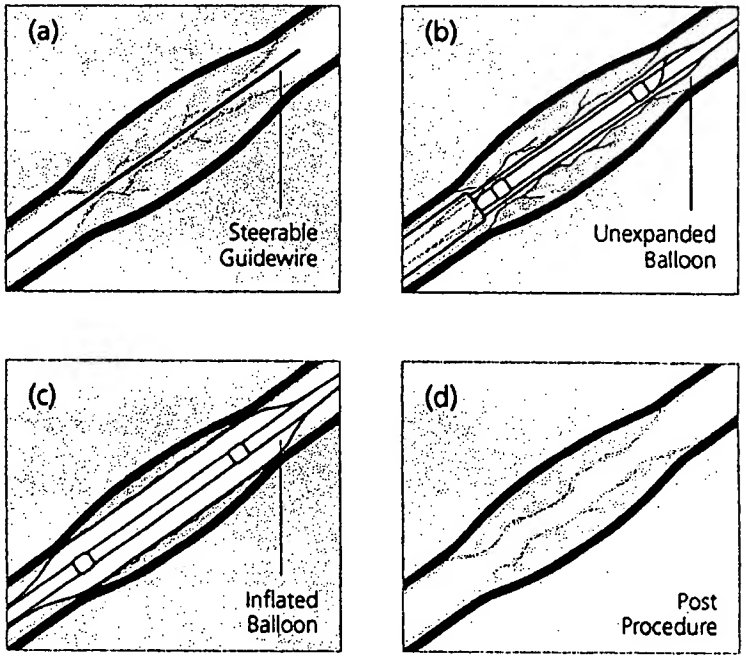
If you have had a cardiac catheterization procedure, angioplasty is similar in many ways. Your heart rhythm will be monitored, an intravenous line will be inserted in your arm, your arm or groin area will be shaved and cleaned and the procedure will be performed through that area. As with cardiac catheterization, it is important for you to follow your doctor's instructions during the procedure.

Balloon Angioplasty Step-by-Step

- After local anesthetic is given, a small incision is made in your arm or groin and a catheter sheath introducer is inserted into the artery. Then, a narrower and longer tube, called a guiding catheter, is passed through the sheath to the heart.
- Contrast dye (x-ray dye) is injected through the guiding catheter to allow the doctor to see the arteries of your heart on an x-ray machine called a fluoroscope.
- While observing the arteries on the x-ray screen, (a) the doctor threads a guidewire through the guiding catheter and advances it to the diseased artery.
- A balloon catheter is inserted over the guidewire (b) and positioned at the site of the blockage.
- Once the balloon catheter is in place, the balloon is expanded (c). As the balloon expands, it compresses the fatty deposits (plaque) against the lining of the artery. The balloon may be expanded one or more times before it is removed. X-ray pictures are taken so that the doctor can monitor your artery as the blood flow is improved.
- Once the balloon catheter is removed, the fatty deposits remain compressed, and blood flow is restored to your heart (d). The balloon procedure may last from 30 to 90 minutes, but varies from patient to patient.

It is not uncommon to experience some discomfort or a pressure sensation in your chest when the balloon is inflated. During the procedure you will be asked to remain very still. You will be asked how you are feeling; be sure to let your doctor know if you experience any discomfort.

Balloon Angioplasty of partially blocked artery.



Coronary Artery Re-narrowing May Occur After Balloon Angioplasty

It is not uncommon for patients to develop a re-narrowing in the same site as the initial balloon procedure. In fact, one-third to one-half of patients who have successful balloon angioplasty will return in the first 4-6 months after the balloon procedure. This kind of narrowing is called "restenosis" and is due to a type of scar tissue formation.

In order to lower the risk for restenosis, your doctor may recommend a procedure called coronary stent implantation. Experience has shown that use of a coronary balloon-expandable stent reduces the rate of restenosis and improves the success rate of balloon angioplasty.

What is a Coronary Artery Stent?

A coronary stent is a small, slotted, metal tube that is mounted on a balloon catheter. It is inserted into your artery after a wider channel has been created by a balloon, and is positioned at the site of the blockage. When the balloon is inflated, the stent expands and is pressed into the inner wall of the artery. The balloon is then deflated and removed with the stent remaining in place. The stent acts as a scaffold that helps to hold the artery open, which improves blood flow and relieves symptoms caused by the blockage.

Magnetic Resonance Imaging (MRI) A diagnostic study similar to a CT or CAT scan which creates an image using electromagnetic waves instead of x-ray.

Restenosis A re-narrowing or blockage of an artery at the same site where angioplasty was previously done.

A stent is a permanent implant that remains in your artery. Over the next weeks, your cells will form a natural covering that will hold the stent securely in place. Persons allergic to 316L stainless steel, polymers (plastics) or sirolimus may suffer an allergic response to this implant. It is important to notify your physician if you have any known metal, plastic or drug allergies. You may be instructed to avoid having an MRI (Magnetic Resonance Imaging) for eight weeks or even longer after your stent implantation to allow for adequate tissue coverage to occur over the stent. Metal detectors found in airports and appliances such as microwave ovens also will not affect the stent or make it move.

Some of the currently available stents are:

- **Uncoated stents** - An expandable, slotted metal tube that acts as a mechanical scaffold in a vessel. The Bx VELOCITY® Stent is an example of an uncoated stent.
- **Coated stents** - A stent with a thin surface covering. The Bx VELOCITY® Stent with heparin coating is an example of a coated stent.
- **Drug-eluting stents** - The CYPHER™ Sirolimus-eluting Coronary Stent is an example of a drug-eluting stent. The CYPHER™ Sirolimus-eluting Coronary Stent contains a drug called sirolimus. A drug-eluting stent allows for the release of that particular drug at the stent implantation site. The action of the drug (sirolimus) is intended to limit the over-growth of normal tissue as the healing process occurs following coronary stent implantation.

How is a Coronary Stent Implanted?

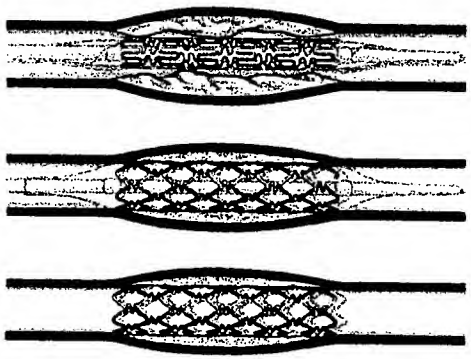
A coronary stent may be placed after the initial balloon procedure, which is done to create a wider opening for the stent. You will have the same feelings when the stent is put in place as when the balloon was expanded during the procedure.

- The stent, which is mounted on a balloon catheter, is inserted into the artery and placed at the site of the initial blockage.
- When the balloon and stent are positioned, the balloon is inflated. The stent expands and becomes firmly pressed into the inner wall of the artery. One or more stents may be used at the site that was narrowed or blocked.
- X-ray pictures are taken so that the doctor can see the stent in your artery. Additional balloon inflations may be needed to fully expand the stent.
- The balloon catheter is deflated and removed along with the guidewire and guiding catheter.
- The stent will remain in place permanently, keeping the artery open.

A stent is mounted on a balloon catheter.

The balloon is inflated and the stent is expanded.

The balloon is removed and the stent is implanted in the vessel.



Coronary Stent Re-narrowing (In-stent Restenosis) May Occur After Coronary Stenting

Occasionally some patients develop a re-narrowing within the stent which may lead to recurrence of symptoms such as feelings of pressure, tightness, or pain in the chest, arm, back, neck or jaw (see also "Symptoms of heart disease"). This kind of narrowing is called "in-stent restenosis" and is due to a type of scar tissue formation. In fact, 10 to 20 percent of patients who have successful stent implantation develop in-stent restenosis over a period of 4-6 months.

To lower the risk of in-stent restenosis, your doctor may recommend implantation of a CYPHER™ Sirolimus-eluting Coronary Stent. Experience has shown that use of the CYPHER™ Stent can reduce the rate of in-stent restenosis and repeat cardiac intervention.

What is the CYPHER™ Sirolimus-eluting Coronary Stent and How Does It Work?

The CYPHER™ Sirolimus-eluting Coronary Stent is designed to prevent re-narrowing from occurring within the stent (in-stent restenosis). It consists of a stainless steel Bx VELOCITY® Coronary Stent with a thin coating of drug (sirolimus) on its surfaces. The drug is located within a polymer (plastic) coating. The Bx VELOCITY® Stent is designed to provide mechanical support in the artery, while the drug (sirolimus) is slowly released into the artery wall around the stent. The action of the drug (sirolimus) is intended to limit the overgrowth of normal tissue as the healing process occurs following coronary stent implantation. Overgrowth of normal tissue is thought to be a major factor responsible for re-narrowing of the artery after stenting.

When Should the CYPHER™ Stent Not Be Used (Contra-indications)?

- If you cannot take aspirin or blood-thinning medications (also called antiplatelets or anticoagulants)
- If you have an allergy to the drug sirolimus, its derivatives or a certain category of polymers known as polymethacrylates or polyolefin.
- If the physician decided that the blockage will not allow complete inflation of the angioplasty balloon.

What Are the Risks and Potential Benefits of Treatment with the CYPHER™ Sirolimus-eluting Coronary Stent?

Potential adverse events which may be associated with the implantation of a coronary stent include: allergic reaction, irregular heart rhythm, death, drug reactions to blood-thinning agents (antiplatelet / anticoagulants) or contrast media, emergency bypass surgery, fever, bleeding at the puncture site, chest pain or angina and stroke.

Potential adverse events related to the drug sirolimus (based on studies of patients who used the drug for a prolonged period of time) include: infection, tumor formation, fatigue, joint pain and diarrhea.

Exposure to sirolimus and the polymer coating is directly related to the number of implanted stents. Use of more than two CYPHER™ Stents has not been adequately evaluated. Use of more than two CYPHER™ Stents will result in your exposure to a larger amount of sirolimus and polymer coating than experienced in the clinical studies.

There is no clinical experience on the performance of the CYPHER™ Stent before or after use of brachytherapy.

The safety and effectiveness of the CYPHER™ Stent was compared to Bx VELOCITY® Stent (an uncoated stent) in the SIRIUS study that included 1058 patients. All patients were followed for 1 year. The study results showed that patients who received a CYPHER™ Stent had a significantly lower incidence of repeat procedures when compared to the uncoated Bx VELOCITY® Stent group. Additionally, patients treated with the CYPHER Stent had an in-lesion restenosis rate of 8.9% while patients treated with the Bx VELOCITY® Stent had an in-lesion restenosis rate of 36.3%. The combined occurrence of death, heart attacks, bypass surgery and repeat angioplasty was 8.3% for CYPHER™ Stent patients and 22.3% for Bx VELOCITY® Stent patients.

The study showed that the risks associated with the CYPHER™ Stent are equivalent to the risks associated with the Bx VELOCITY® (uncoated) Stent.

Long term risks and benefits (i.e. greater than 1 year) associated with the CYPHER™ Stent are currently unknown.

Antiplatelet A medicine that reduces the clumping of platelets in the blood. An antiplatelet medicine helps thin the blood to prevent clot formation.

Brachytherapy The administration of a therapeutic dose of radiation from within a vessel to a specific area of vascular disease to prevent the reoccurrence of an obstruction or narrowing.

In-stent Restenosis A re-narrowing or blockage of an artery within a stent.

Other Treatment Options

Other treatment options include balloon angioplasty, placement of other stents or bypass surgery.

- Balloon Angioplasty – See "Balloon Angioplasty" section. This may include the use of an angioplasty catheter or other devices that are intended to open the obstruction or narrowing of the blood vessel.
- Uncoated Stents – An expandable, slotted metal tube that acts as a mechanical scaffold in a vessel. The Bx VELOCITY® Stent is an example of an uncoated stent.
- Coated stents - A stent with a thin surface covering. The Bx VELOCITY® Stent with heparin coating is an example of a coated stent.
- Bypass surgery – An operation in which a piece of vein or artery is used to bypass a blockage in a coronary artery.

Preparation for a CYPHER™ Sirolimus-eluting Coronary Stent

If you know in advance that you will be receiving a CYPHER™ Sirolimus-eluting Coronary Stent, your doctor will ask you to follow certain instructions. For several days before the procedure, you may be asked to take aspirin and other prescribed medications.

Caution: Be sure to let your doctor know

- If you are taking any other medications
- If you have a history of bleeding problems
- If you have any metal allergies (i.e., 316L stainless steel)
- If you are allergic to the drug Rapamune®[1] (sirolimus), its derivatives or a certain category of polymers known as polymethacrylates or polyolefin.

- If you are currently taking Rapamune®
- If you are currently or think you may be pregnant
- If you are currently nursing

Note: Sirolimus is also available in tablet and liquid form, known by the name Rapamune®. Let your doctor know if you are currently using this drug.

How is Treatment with the CYPHER™ Sirolimus-eluting Coronary Stent Performed?

Placement of a CYPHER™ Sirolimus-eluting Coronary Stent is no different from the placement of an uncoated stent, described earlier in this booklet. You will be brought to the cardiac catheterization laboratory and prepared for your heart catheterization. The CYPHER™ Stent will be placed after the initial balloon procedure, which is done to create a wider opening for the stent. You will have the same feelings when the stent is put in place as when the balloon was expanded during the procedure.

- The stent, which is mounted on a balloon catheter, is inserted into the artery and placed at the site of the initial blockage.
- When the balloon and stent are positioned, the balloon is inflated. The stent expands and becomes firmly pressed into the inner wall of the artery. One or more stents may be used at the site that was narrowed or blocked.
- X-ray pictures are taken so that the doctor can see the stent in your artery. Additional balloon inflations may be needed to fully expand the stent.
- The balloon catheter is deflated and removed along with the guidewire and guiding catheter.
- The stent will remain in place permanently.

1. *Rapamune is a registered trademark of Wyeth Pharmaceuticals*

How Long is the Hospital Stay?

Your hospital stay will be the same as for an angioplasty or non drug-eluting stent procedure. Many patients are able to go home the day following the procedure. The amount of time that you may stay in the hospital will depend on several factors including any difficulties that you may have experienced during the procedure and how well the puncture site is healing. The amount of time depends on your physician's discharge orders.

What Happens After Your Angioplasty or Stent Procedure?

After your procedure, you will be moved to a special care unit where nurses will be able to monitor your heart rhythm and blood pressure very closely. At this time, the catheter sheath introducer (tube) may be removed and pressure will be applied to the puncture site, either your groin or arm, until the bleeding has stopped. Your puncture site will be watched closely for any signs of bleeding. If your leg was used to insert the catheters, you may be instructed to lie flat for several hours, and you may not be allowed to bend the leg that was used. Should you see any blood or feel warmth at the area of the puncture site, notify your nurse immediately. Your extremity will be monitored for any changes in color, temperature and sensation.

Once you have returned to your room, you may be able to eat and drink and your family may visit depending on your doctor's orders. Eat foods that are light until you are able to sit upright. Drink all of the fluids that are offered, because they will help to flush the x-ray dye through your kidneys and out of your body. Your doctor will advise you when you can get out of bed and walk.

Many patients are able to go home the day following the procedure. The amount of time that you may stay in the hospital will depend on several factors including any difficulties that you may have experienced during the procedure and how well the puncture site is healing. The amount of time depends on your physician's discharge orders.

Taking Your Medications is Important

Caution:

- After you leave the hospital you may be instructed to take medications. It is very important that you take your medications exactly as prescribed.
- Be sure not to miss any doses.
- Call your doctor if you feel that you cannot tolerate your medications or develop any side effects such as bleeding, upset stomach, rash, or have any questions.

Depending on which blood thinning medications (also called antiplatelet or anticoagulants) are prescribed, you may need to have follow-up blood tests to monitor the effects of the medicine on your blood. This can be done at your local hospital laboratory or primary care doctor's office and you may have breakfast before having the blood taken.

Anticoagulant A substance that slows, suppresses or prevents the clotting of blood.

Caution. It is Very Important to Follow These Instructions:

1. Follow your medication schedule exactly to avoid possible complications related to stent implantation.
2. Do not stop taking any of the prescribed medications unless you are instructed to do so by the doctor who performed the procedure.
3. Notify your doctor immediately if you experience chest pain (angina) or notice any changes such as more severe or frequent chest discomfort, especially in the first month after a procedure. These symptoms may indicate a re-narrowing in your coronary arteries.
4. Notify your doctor if you experience any side effects of the medications such as nausea, vomiting, and bleeding or rash.
5. Show your identification card (see also "After you go home" section) if you report to an emergency room. This card identifies you as a stent implant patient.
6. Keep all appointments for follow-up care including your blood tests.
7. Contact your physician before you have a Magnetic Resonance Imaging (MRI) medical scan. You may be instructed to avoid having an MRI for eight weeks or even longer after your stent implantation to allow for adequate tissue coverage to occur over the stent.
8. Notify your cardiologist or family doctor if you are scheduled to see the dentist in the first month after your procedure. Your physician may prescribe antibiotics to avoid the potential of an infection.

You will be discharged to the care of your cardiologist or family doctor. After returning home, if you experience any pain, discomfort, bleeding of any kind, rash or itching, contact your doctor or the hospital. You should be able to return to your normal activities such as work, sports, and sex very soon. Check with your physician prior to doing anything that is physically strenuous.

After You Go Home

If you received a stent (uncoated, coated or drug-eluting) you will be given a small wallet-size identification card containing information about the location of your stent or therapy and the date it was performed, along with important doctors' names and telephone numbers. An example of the card is included in the back of this booklet; this card should be kept with you at all times. It is important to alert any doctor that is treating you that you received an uncoated, coated or drug-eluting stent.

Follow-up Visits

You may be instructed to return to see your cardiologist or family doctor. The first visit will usually take place within the first 2-4 weeks after your procedure and every six months for the first year. If you are doing well, the doctor may recommend yearly visits thereafter.

Diet and Lifestyle Changes

To help yourself stay healthy in the future, you are encouraged to make important diet, exercise and lifestyle changes. Some patients may need few modifications while others may need to make many changes. Those patients who are able to reduce the fats and cholesterol in their diets are less likely to redevelop blockages within the stent. A low-fat, low-cholesterol diet can lower the levels of fat in your blood and reduce your risk. Eating healthy foods in the right portions will also help you to maintain or achieve a healthy weight.

In addition to a healthy diet, it is extremely important to avoid smoking. Smoking not only increases the risk of worsening coronary artery disease, but it increases the chance that your

PTCA or stent site will close. If you need help with quitting, notify your health care provider.

Other factors that can contribute to heart disease such as stress and lack of exercise should also be evaluated. Steps can be taken to reduce stress in your life and your physician can help you develop a controlled exercise program.

Even after your full recovery, your doctor may want to check your progress from time to time. You can reduce your risk of developing future disease by making healthy lifestyle choices. Be sure to contact your doctor or health care provider if you have any questions or need assistance regarding your lifestyle modifications.

Summary

You have a very important role to play in order to ensure that your procedure will be successful. It is essential that you cooperate with your physician and follow through with your responsibilities as part of the patient/medical team. If you have any questions or concerns, please contact your physician to discuss them. It is important that you get the most benefit from your treatment and join the thousands of people with coronary artery disease who are leading healthy, productive lives.

For more information on patient education, please visit our website: www.CYPHERUSA.com.

Glossary

Angina (Pectoris) - Chest discomfort, pain, tightness or pressure. May also have associated pain in neck, jaw, back or arm. May include profuse sweating, nausea, or shortness of breath. Angina may be a single symptom or a combination of these symptoms.

Angioplasty - A balloon procedure to open an obstruction or narrowing of a blood vessel. Also known as percutaneous transluminal coronary angioplasty (PTCA).

Anticoagulant - A substance that slows, suppresses or prevents the clotting of blood.

Antiplatelet - A medicine that reduces the clumping of platelets in the blood. An antiplatelet medicine helps thin the blood to prevent clot formation.

Atherosclerosis - A disease process in which fatty substances (plaque), such as cholesterol, are deposited on the inner lining of blood vessels.

Brachytherapy - See Intravascular Brachytherapy

Coronary Artery Bypass Graft (CABG) Surgery - An operation in which a piece of vein or artery is used to bypass a blockage in a coronary artery; performed to prevent myocardial infarction and relieve angina pectoris.

CAD - Coronary Artery Disease.

Cardiac - Relating to the heart.

Cardiac Catheterization - *See Coronary Angiogram.*

CAT Scanning - *See Computered Tomography Scanning.*

Catheter - A tube used for gaining access to one of the body's cavities or blood vessels. In angioplasty, a catheter provides access to the heart's arteries.

Catheterization - A procedure that involves passing a tube (catheter) through blood vessels and injecting dye to detect blockages.

Cholesterol - A substance that circulates in the blood and plays a role in the formation of blockages. Cholesterol originates in foods that are rich in animal fats.

Computered Tomography Scanning - A technique for producing cross-sectional images of the body in which X-rays are passed through the body at different angles and analyzed by a computer; also called CT scanning or CAT scanning.

Coronary - Related to the arteries that supply blood to the heart.

Coronary Angiogram - A test used to diagnose CAD using the catheterization procedure. Contrast dye is injected into the coronary arteries via a catheter, and this allows the doctor to see, on a x-ray screen, the exact site where the artery is narrowed or blocked.

Coronary Arteries - The coronary arteries are special blood vessels which supply the heart with necessary oxygen and nutrients. The heart does not function properly without enough oxygen.

Coronary Artery Disease - Atherosclerosis of the coronary arteries.

CT Scanning - *See Computer Tomography Scanning.*

Diabetes - A disease affecting one's metabolism of glucose (sugar) which causes changes in blood vessels. These changes may aid in the development of coronary artery disease.

EKG - Electrocardiogram. A test that measures and shows the electrical activity of the heart muscle.

Exercise Electrocardiogram - *See Stress Test.*

Fluoroscope - Equipment used in a cardiac catheterization procedure which captures a "motion picture" x-ray image of the heart and coronary arteries.

In-stent Restenosis - A re-narrowing or blockage of an artery within a stent.

Intravascular Brachytherapy - The administration of a therapeutic dose of radiation from within a vessel to a specific area of vascular disease to prevent the reoccurrence of an obstruction or narrowing.

Ischemia - Lack of or insufficient oxygen to the tissue, in this case, to the heart muscle. Ischemia is a reversible condition if normal blood flow is restored.

Left Ventricle - The largest chamber of the heart which is responsible for pumping blood throughout the body.

Lesion - A blockage in a blood vessel. It is also known as a plaque or stenosis.

MRI - Magnetic Resonance Imaging. A diagnostic study similar to a CT or CAT scan which creates an image using electromagnetic waves instead of x-ray.

Myocardial Infarction - Commonly called a "heart attack". Involves irreversible damage to heart tissue/muscle. Insufficient oxygen reaching the heart muscle via the coronary arteries may cause angina, heart attack (myocardial infarction), or even death to the affected area of the heart.

Percutaneous - Performed through a small opening in the skin.

Percutaneous Transluminal Coronary Angioplasty - *See Angioplasty.*

Plaque - The accumulated material that causes a blockage in a blood vessel. Also known as a lesion or stenosis.

Platelets - Blood cells that are involved in the formation of a clot.

PTCA Percutaneous Transluminal Coronary Angioplasty - *See Angioplasty.*

Restenosis - A re-narrowing or blockage of an artery at the same site where angioplasty was previously done.

Stenosis - A narrowing of any canal, especially one of the cardiac vessels.

Stent - An expandable, slotted metal tube, inserted into a vessel. A stent acts as a scaffold to provide structural support for a vessel.

Stress Test - A test that measures electrical changes in the patient's heart (EKG) while the patient is doing controlled exercise. The stress test can show if there has been damage to the heart or if there is decreased blood flow to areas of the heart.

Thrombosis/Late Thrombosis - A blockage caused by clumping of cells. Late Thrombosis occurs after 30 days.

Transluminal - Through the inside opening of an artery.

Triglycerides - Substances in the blood that are a component of the "bad" type of cholesterol.

Vessel - Any channel for carrying a fluid, such as an artery or vein.

Notes

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WYETH

In re: U.S. Patent No. 5,563,146

Issued: October 8, 1996

Titled: METHOD OF TREATING HYPERPROLIFERATIVE VASCULAR DISEASE

Inventors: RANDALL E. MORRIS and CLARE R. GREGORY

Customer Number: 25291

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

POWER OF ATTORNEY

Wyeth, the assignee of record of the above-identified patent hereby appoints:

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as its attorney to transact all business in the United States Patent and Trademark Office in connection with the Application for Patent Term Extension.

Wyeth

Gale Matthews
Assistant Secretary

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